

PRIMARY LUNG CARCINOMA.

by

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Appendix (details of cases)

Separate volume.



## INTRODUCTION.

The following observations are based on an investigation of 212 cases of intrathoracic neoplasms that have occurred during the past 31 years at the Royal Infirmary of Edinburgh. The study was pursued mainly from the pathological stand point of view. In all, 38 cases were examined fairly completely macroscopically and microscopically and to this group of cases the term "group A" has been given; 57 cases were examined microscopically only and these plus the 38 cases mentioned above form "group A.B" which consists of 95 cases. In the remaining 117 cases with the exception of one or two, a pathological report but no sections, existed. These 117 cases form "group C".

HISTORICAL.

"It is good occasionally to unroll the pages of the past, and to endeavour to discover the successive steps by which the existing state of things has been brought about."

The Early History of the Medical Profession in Edinburgh, by Dr. John Gairdner, 1864.

According to Adler, lung tumours were absolutely unknown in ancient and mediaeval medicine until Morgagni (1682-1772) laid the foundations of pathological anatomy. Morgagni described the disease of a man 60 years old, which was accompanied by cough and copious expectoration of a yellowish, rather crude material, rarely, but then distinctly, stained by streaks of blood. At autopsy the lung was found extremely hard, adherent to pleura and mediastina, and nothing else but an "ulcus cancrum" in the right lung. Adler considers this to be a case of primary lung tumour.

John Forbes, the translator of Loennec's treatise on the diseases of the chest and on mediate auscultation, believes that lung cancer was discovered independently in different centres. I quote the following paragraph from his book published over a century ago: "Among other discoveries of the first years of his/



his (Loennec) labours in the dissecting room, the morbid alterations named by him, Encephaloid Cancer and Melanosis, deserve particular notice for their importance. Both these are mentioned by him in the memoir read before the School of Medicine in 1805; and although it is true that the former was previously well known in England, having been described by Burns in 1800 (John Burns of Glasgow), by Hey in 1803 (Mr. Hey of Leeds) and by Abernethy in 1804 (London), the subject of our memoir (Loennec) appears to have been totally ignorant of this fact, and is, therefore, equally entitled with these gentlemen to the honour of having discovered it."

In the opinion of John Forbes, the best and most complete account on the subject at that time was given by Mr. Wardrop in his "Observations on Fungus Haematodes or Soft Cancer", published in 1809.

The subject was given little attention and primary cancer of the lung used to be regarded as a condition of great rarity until in 1912 Adler was able to publish a monograph on the subject with a review of 374 cases collected from the literature. Since that time the writings have been numerous and the bibliography has increased on every side so that a comparatively large series can be studied.

Professor Turnbull in a personal interview\* informed/

\*Summer of 1934.



informed me that for many years he held the view that primary malignant disease of the lungs and bronchi were nearly all carcinomata and that the so-called oat-celled sarcomata were in reality carcinomata.

In 1926, Bernard published a classical paper in which he confirmed Professor Turnbull's views on the carcinomatous nature of the oat-celled tumours.

This was also subsequently confirmed by Duguid in 1927 and Shennan in 1928.

It may be useful to point out, that the earlier writers on this subject described the oat-cell growths as carcinomatous. Thus, I quote the following from Maxwell's paper published in 1930: "It is interesting to note the complete reversal of opinion which has occurred within the last 40 years. In the histological reports of the older cases from the earliest time at which such reports were added to the notes, these growths were described as carcinomatous. Such cases were reported by Percy Kidd in 1883, while R.F.Jowers, writing in 1887, discusses the nature of bronchial growths and states that of the cases recorded in the medical journals of the time only one is classed as a sarcoma, the remainder being described as encephaloid cancer. In the earlier years of the present century it became customary to divide intra-thoracic new-growths into two varieties: obvious carcinomata/

carcinomata, composed of columnar or squamous cells, and a large group of tumours composed of smaller cells which were variously described as "alveolar", "spindle-celled" or "oval celled" sarcomata".

Lastly, I should like to point out the fact that in studying the cases of intrathoracic neoplasm which occurred between the years 1904-1934 inclusive, I have come across statements in the histological descriptions which would point to an undecided opinion as to what the nature of the growth was. Thus, Dr. Alexander describing the histological features of a case in 1924 (Case No.109) wrote: "There has been a good deal of discussion over the histological features of this tumour. The consensus of opinion is that it is a carcinoma, primary in bronchial mucosa. It has assumed an undifferentiated character, however, and resembles a sarcoma very closely." No sections are available but from the above statement, Dr. Alexander, was, undoubtedly, dealing with an oat-cell bronchial carcinoma. A few other statements may be quoted:

- 1924 (Case No.114) "Peculiar growth. Appears carcinomatous".
- 1920 (Case No.128) "The growth is very cellular with a definite perithelial arrangement, being related to definite well formed blood vessels."
- 1908 (Case No.190) "All the nodules of the new-growth are of the nature of lymphosarcoma. In those within the pancreas, there is some alveolar arrangement."



INCIDENCE.

In 1912, after an extensive review of the literature, Adler collected 374 cases of carcinoma of the lung. He noted then, that "on one point, however, there is nearly complete consensus of opinion, and that is that primary malignant neoplasms of the lungs are among the rarest forms of disease." Since then, there has appeared a considerable amount of literature attesting to the increased frequency of this condition. This has emanated from various centres, both in Europe and in America and it has been thought that a similar increase was noticeable in Edinburgh. In order to ascertain so far as possible, the actual state of affairs, it was decided to make an investigation and analysis of all the cases which have been entered in the autopsy registers at Edinburgh Royal Infirmary. The records from 1904 to 1934 inclusive, have been carefully searched and every case where intrathoracic neoplasm was reported has been noted and considered. From amongst them have been chosen only those cases in which the evidence was conclusively in favour of their being primary intrathoracic neoplasms.

To leave no place for doubt, as this has already been expressed by Rosahn, Bonser and others, as to the meaning/



meaning of the term "intrathoracic neoplasm", it should be stated here, that only those cases were included, which were described as malignant and as arising from lung or mediastinal glands and that cases of Hodgkin's disease and cancer of the oesophagus were definitely excluded.

TABLE I.

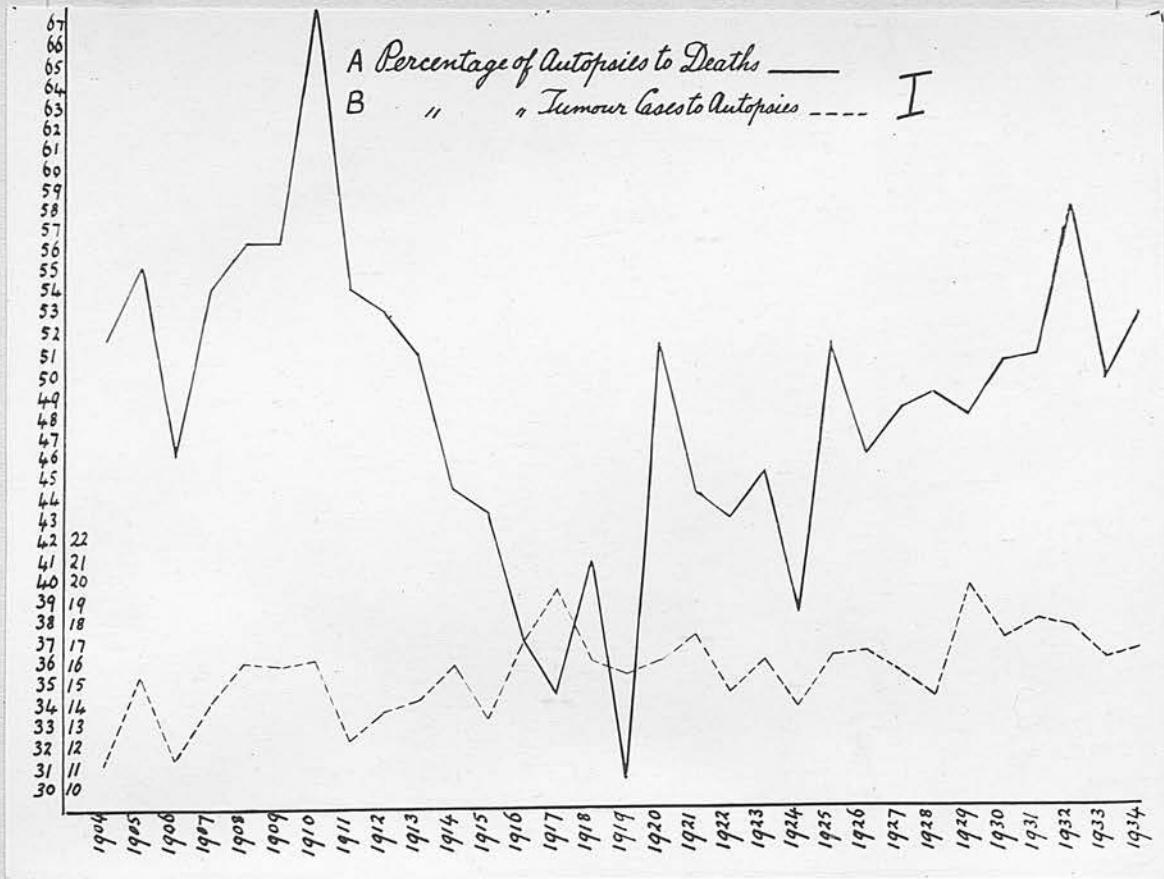
Year	1 No. of Admissions	2 No. of Deaths	3 No. of Autopsies	4 % of Autopsies to deaths	5 No. of Tumour Cases	6 No. of intra- thoracic Tumours	7 % of Tumours to autopsies	8 % Intrathoracic Tumours	9 Tumours Autop.	10 Admi.	11 Deaths
1904	10403	858	435	51.9	49	4	11.3	8.2	0.8	0.03	0.4
1905	10226	792	440	55.5	68	3	15.5	4.4	0.5	0.02	0.3
1906	10430	820	380	46.3	44	3	11.6	6.8	0.7	0.02	0.3
1907	10340	815	442	54.3	61	5	14.1	8.2	1.1	0.04	0.6
1908	10975	823	467	56.7	75	8	16.1	10.7	1.7	0.07	0.9
1909	11566	831	472	56.7	76	4	16.0	5.3	0.8	0.03	0.4
1910	11523	775	531	68.5	87	10	16.2	11.5	1.9	0.08	1.2
1911	11805	877	478	54.5	60	4	12.5	6.6	0.8	0.03	1.4
1912	11895	838	448	53.4	62	2	13.9	3.2	0.4	0.01	0.2
1913	11691	870	448	51.4	64	7	14.3	10.9	1.6	0.05	0.8
1914	11988	890	399	44.8	64	8	16.0	12.5	2.0	0.06	0.8
1915	12352	909	396	43.5	54	3	13.6	5.6	0.8	0.02	0.3
1916	11553	836	314	37.5	54	5	17.2	9.2	1.6	0.04	0.5
1917	11181	847	295	34.8	58	4	19.7	6.9	1.4	0.03	0.4
1918	11646	795	325	41.1	53	7	16.3	13.2	2.2	0.06	0.8
1919	11680	1020	313	30.6	49	3	15.6	6.1	1.0	0.02	0.2
1920	12521	906	469	51.7	76	8	16.3	10.5	1.7	0.06	0.8
1921	12814	885	394	44.5	69	5	17.5	7.7	1.3	0.03	0.5
1922	13372	928	402	43.3	60	5	14.9	8.3	1.2	0.04	0.5
1923	14231	931	454	45.5	74	6	16.3	8.1	1.3	0.04	0.6
1924	14883	970	478	38.9	67	5	14.0	7.5	1.0	0.03	0.5
1925	14908	1052	544	51.7	91	7	16.7	7.7	1.3	0.04	0.6
1926	16138	1107	514	46.4	87	4	16.9	4.6	0.7	0.02	0.3
1927	17843	1115	545	48.8	87	7	15.9	8.0	1.2	0.03	0.6
1928	18779	1084	536	49.4	79	6	14.7	7.5	1.1	0.03	0.5
1929	19001	1244	602	48.4	121	15	20.0	12.4	2.4	0.07	1.2
1930	19626	1262	644	51.0	113	9	17.5	7.9	1.3	0.04	0.7
1931	19184	1129	579	51.2	107	10	18.4	9.3	1.7	0.05	0.8
1932	19145	1197	699	58.3	126	12	18.0	9.5	1.7	0.06	1.0
1933	19271	1263	632	50.0	105	15	16.6	14.2	2.3	0.07	1.1
1934	18943	1249	667	53.4	114	18	17.0	15.7	2.6	0.09	1.4

Before considering the above figures (Table I)

it/

it is necessary to point out that the percentage of autopsies to deaths is the same throughout the 31 year period and on an average of 48.6 per cent (see Table I, column 4 and Graph I A). For no known

GRAPH I A.B.



reason, there occurred a sudden rise to 68.5 per cent in 1910, but this was not sustained and fell back to normal in 1911, then this was followed by a fall to 43.5%, 37.5%, 34.8%, 41.1% and 30.6% in 1915, 1916, 1917, 1918 and 1919 respectively which was approximately the war period; thereafter the curve began to/



to take its previous form.

The fact that a fairly constant percentage of cases autopsied throughout the entire period under review, is of significance as it would answer the criticism that post-mortem figures are unreliable owing to the tendency to select only certain cases for examination.

The second important point to note (see Table I, column 7 and Graph I B.) is the fact that the percentage of tumour cases in all sites to autopsies has, also, been the same throughout the 31 year period (average 15.7%), a point which is in agreement with the results published by the Registrar General for Scotland in which it was shown that there was no real increase of cancer at the present day.

These two points (percentage of autopsies to deaths and percentage of tumour cases to autopsies) being constant, will certainly help to find out the actual state of affairs in Edinburgh and whether the increase is apparent or real. And now, I proceed to the statistical study of intrathoracic neoplasm in relation to autopsies, to malignant tumours in all sites, to admissions and to deaths.

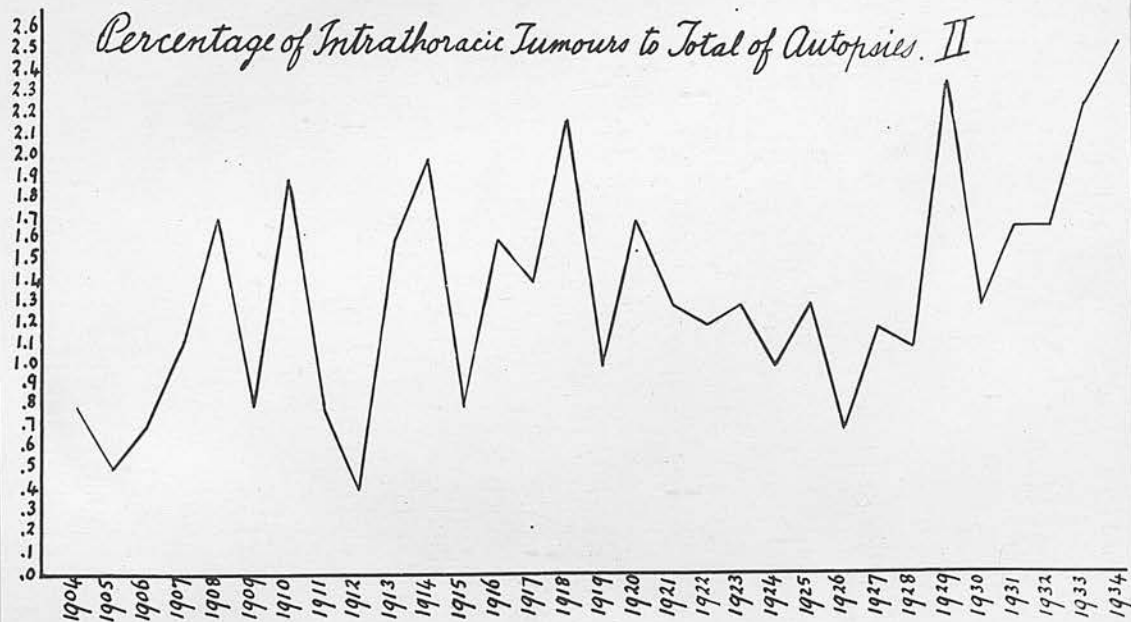
(a) In Relation to Autopsies.

During the 31 year period 1904-1934, 212 cases of intrathoracic tumours have come to post-mortem at the/



the Royal Infirmary. This represents an average ratio of intrathoracic tumours to all autopsies of 1.3 per cent. (See Table I, column 9 and Graph II). It is to be noted that although there is considerable

GRAPH II.



variation in the actual number of intrathoracic tumours occurring from year to year, there is no evident percentage increase throughout the period under review except in the year 1934 in which it reached 2.6%, but as it is only just slightly higher than/

than that recorded for 1914 (2.0%), 1918 (2.2%) and 1929 (2.4%) following which in each year there occurred a sudden fall to below the average percentage of the entire 31 year period stated above (1.3%), it is unlikely to be of significance unless it continued and was sustained for several more years.

Studying the curve in Graph II more closely, it can be seen that following Barnard's paper published in 1926, there occurred a rise from 0.7% in 1926 to 1.2% and 1.1% in 1927 and 1928 respectively, and a sudden but unsustained rise in 1929 which reached 2.4%. This was evident from the change in the nomenclature found in the post-mortem registers namely a change from mediastinal lymphosarcoma to oat-cell bronchial carcinoma. The rise in 1929, however, was not sustained as it fell in the following year to the normal average of 1.3% which is the average percentage throughout the 31 year period. Then, the curve started to rise but rather gradually to 1.7% both in 1931 and 1932 and to 2.3% in 1933 and 2.6% in 1934.

During the period 1931-1934 which marks the period of slight, but rather gradual rise there occurred two factors which undoubtedly added partly if not entirely to this slight but rather gradual rise. These two factors were firstly, the coming to Edinburgh of/

of Professor Drennan who collected and kept practically every case of intrathoracic tumour that came to the post-mortem room with the intention of further study; secondly, the taking up of the subject by me for a special study during the last two years. It may be added that the interest of the University and Infirmary Staff was apparent and may be judged from Case No.3, Miscellaneous Group (see Plate I) which occurred in 1932. This case, because of absence of dysphagia and

PLATE I.



and the X-ray appearances of the chest, was clinically diagnosed/

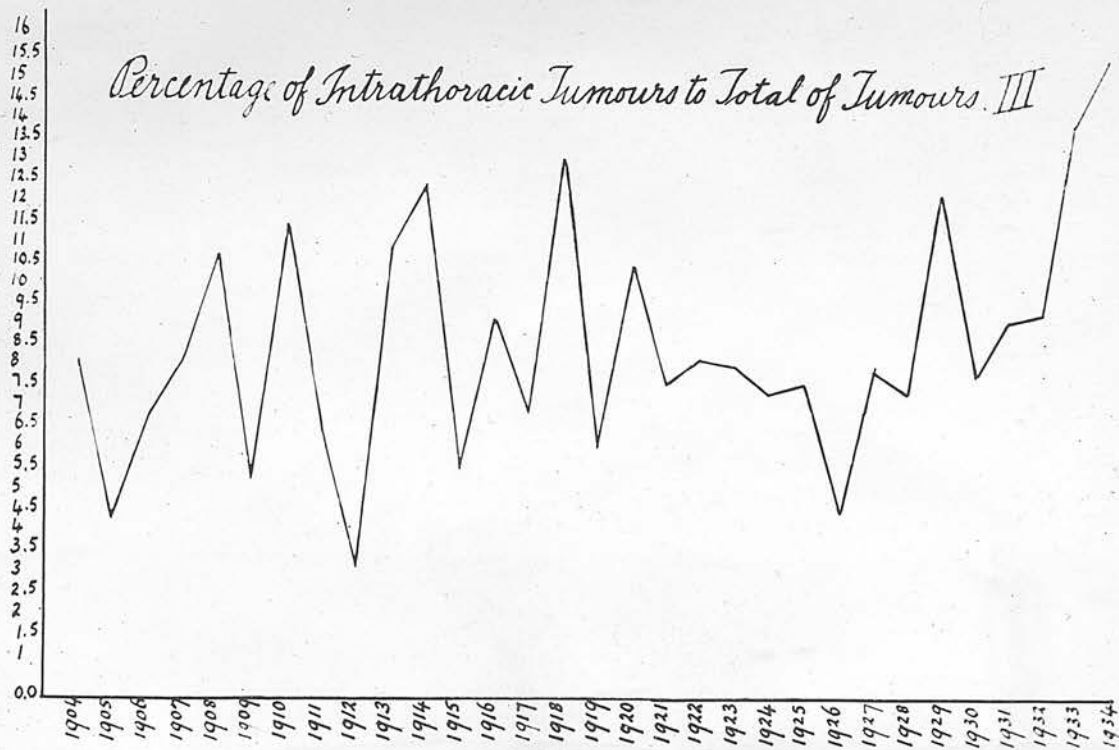


diagnosed as one of bronchial carcinoma and this was agreed upon by the pathologist in charge; however, when the case was subjected to thorough examination its true nature was revealed and it proved to be a rather rare oesophageal growth, namely an adenocarcinoma arising primarily from the oesophagus and invading the mediastinum and the pleura in relation to the right upper lobe. The entire bronchial tree was free of growth.

(b) In Relation to Malignant Tumours in all Sites.

The relation of intrathoracic tumours to tumours in all sites is an average of 8.3% (see Table I, column 8 and Graph III).

GRAPH III.



Again, there is no evident percentage increase throughout the period under review except in the years 1933 and 1934 in which it reached 14.2% and 15.7% respectively, but again as these figures are just slightly higher than those recorded for 1914 (12.5%) and 1918 (13.2%) and 1929 (12.4%) after which in each year a fall to below the average (8.3%) occurred, they are unlikely to be of significance unless the rise was continued and sustained for several more years.

(c) In Relation to Admissions.

Another method of estimating the incidence of intrathoracic tumours is by means of its relation to the number of cases admitted to the hospital wards.

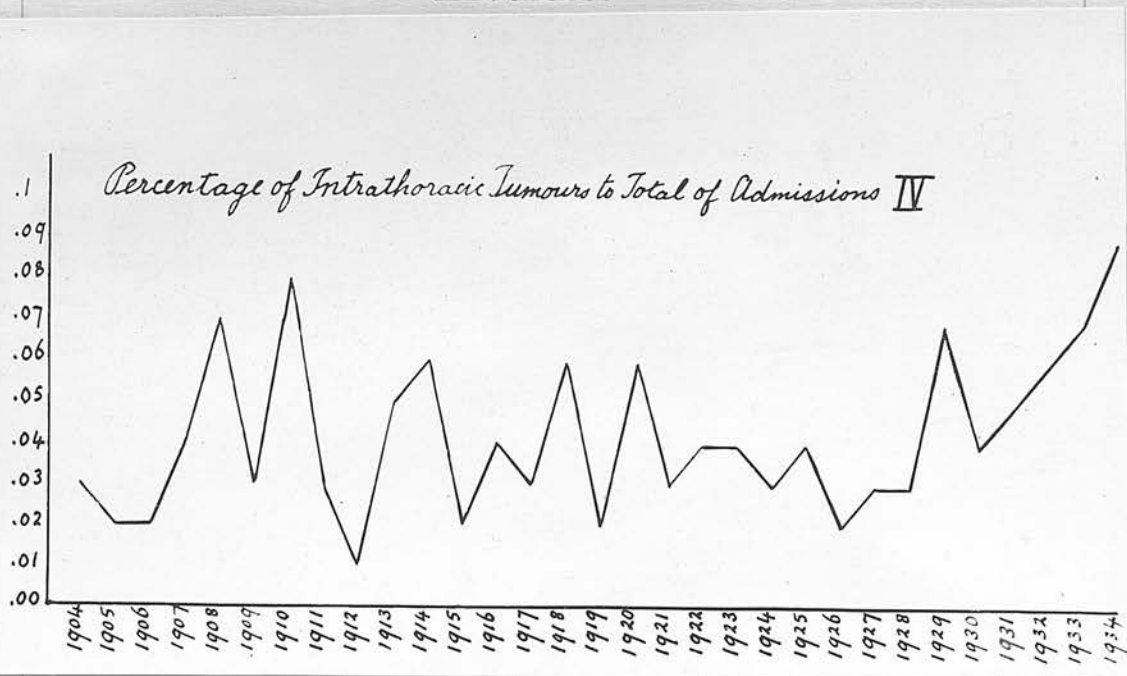
The arguments produced in favour of a real increase in intrathoracic neoplasms are based upon the rise in the curves representing the ratio between the actual cases which are autopsied and the total number of post-mortems performed. Professor Passey of Leeds (also, in a personal interview\*) pointed out that conclusions drawn from this ratio alone are apt to be misleading. According to Professor Passey's observations, the curve of incidence of intrathoracic neoplasm shows no marked increase or none at all when the percentage is calculated in relation to the total admissions/

\* Summer of 1934.

admissions per annum of patients to hospital. He pointed out that the total admissions per annum were considerably more than double in comparison with the pre-war period, and if the annual admission list be taken as he claims to be a more reliable criterion than the total autopsy record, the figure for intra-thoracic neoplasm based on the autopsy record alone should be halved if the truth is to be reached in regard to the incidence of the disease.

Accordingly, the percentage of intrathoracic tumours to admissions to the hospital wards is an average of 0.04% (see Table I, column 10 and Graph IV). Graph IV shows more clearly the fact that

GRAPH IV.



there is no evident percentage increase throughout the/

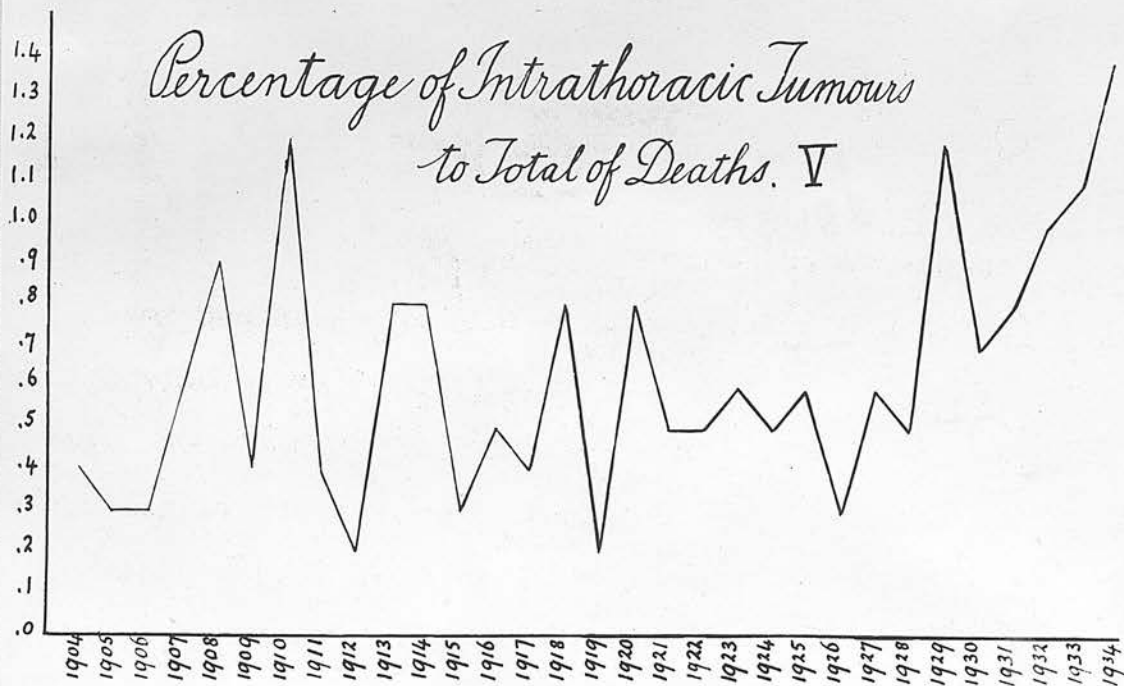


the period under review except in the year 1934 in which it reached 0.09%, but as it is only slightly higher than that recorded for 1910 (0.08%), it is unlikely to be of any significance unless the rise was continued and sustained for several more years.

(d) In Relation to Deaths.

Another method of estimating the incidence of intrathoracic tumours thought of, is by means of its relation to the number of deaths in the hospital wards, (see Table I, column 11 and Graph V).

GRAPH V.



The percentage of intrathoracic tumours to deaths in the hospital wards is an average of 0.6%. Graph V in its turn, shows the fact arrived at from the previous graphs, namely that there is no evident percentage increase throughout the period under review except in the year 1934 in which it reached 1.4%, but as it is only slightly higher than those recorded for 1910 and 1929 (1.2%), it is unlikely to be of any significance unless it continued for several more years.

TABLE II.

Year	% of Autopsies to Deaths	% of Tumours to Autopsies	% of Intrathoracic Tumours to Total of:			
			Tumours	Autopsies	Admissions	Deaths
1904-1908	52.5	13.7	7.6	0.9	0.03	0.5
1909-1913	56.9	14.5	7.5	1.1	0.04	0.6
1914-1918	40.3	16.5	9.4	1.6	0.04	0.5
1919-1923	43.1	16.5	8.1	1.3	0.03	0.5
1924-1928	47.0	15.6	7.0	1.0	0.03	0.5
1929-1933	51.8	18.1	10.6	1.9	0.06	0.9

In Table II the figures are expressed as percentages in period of 5 years. Here, again, there is no evident percentage increase throughout the period under review (1904-1933) except in the last 5 year period. The rise is sudden and is undoubtedly due to the factors discussed previously under Table I (in Section (a) Relation to Autopsies) and it is unlikely to be of any significance unless it continued and was sustained for several more years.

(e) Comparison of Incidence in Various Sites.

In 1932 Wilhelm Peters pointed out that although the incidence of cancer in all sites at post-mortem is not increasing to any great extent, the marked rise in lung cancer has been compensated by a fall in stomach cancer. The accuracy of this observation by Peters was questioned and commented upon in 1934 by Bonser in Leeds. Bonser found that, there has been remarkably little variation in the incidence of cancer in the common sites such as large intestine, rectum, oesophagus, brain, pancreas and gall-bladder. Also, this point has been touched upon and my results are in agreement with those published by Bonser (see Table III and Graph VI).

TABLE/

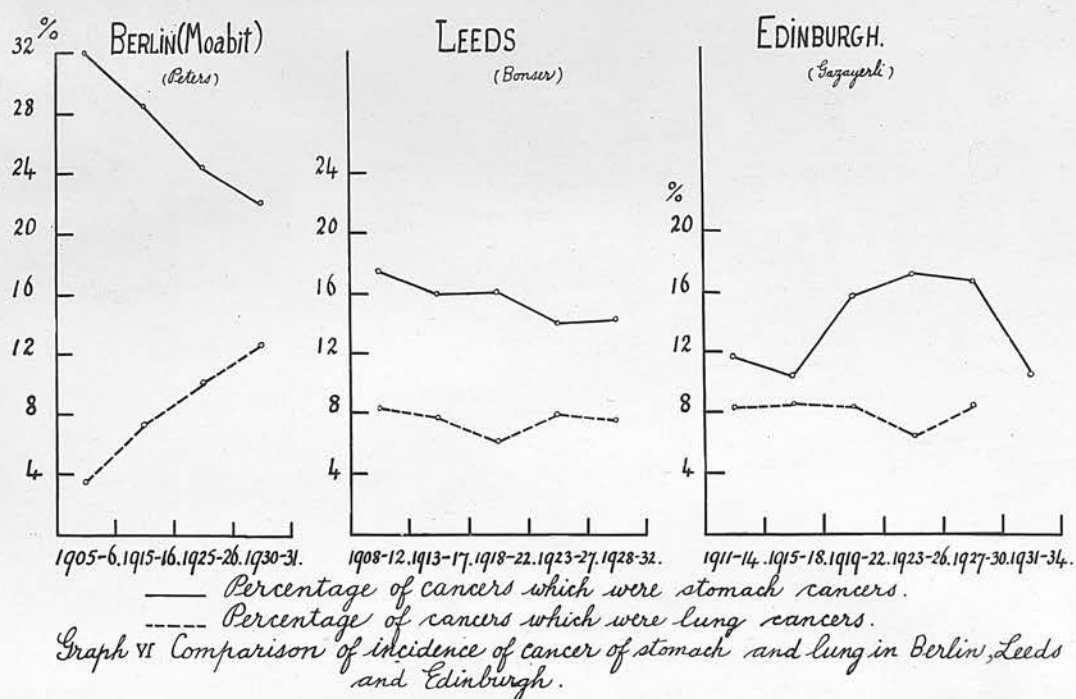


TABLE III.

## Comparison of incidence of cancer in various sites at P-M.

Year	Total Tumor (Cancers)	Intrathoracic.		Stomach.		Liver (Primary)		Gall-bladder.		Pancreas		Rectum		Sigmoid Flexure.	
		No	%	No	%	No	%	No	%	No	%	No	%	No	%
1911-1914	250	21	8.3	29	11.5	3	1.1	7	2.2	7	2.7	9	3.6	18	6.5
1915-1918	219	19	8.7	24	10.8	16	7.2	4	1.7	21	9.9	9	4.0	11	4.9
1919-1922	254	21	8.1	42	15.9	5	2.1	9	3.5	19	7.3	9	3.4	7	2.8
1923-1926	319	22	6.9	58	17.9	9	2.8	3	0.9	29	9.6	18	5.4	20	5.9
1927-1930	400	37	8.9	71	17.3	7	1.6	8	1.8	16	3.8	9	2.2	17	4.0
1931-1934	452	55	12.1	50	10.8	5	1.0	8	1.7	12	2.6	9	1.9	25	5.5

GRAPH VI.



From/

From the above detailed study it may be concluded that an analysis of post-mortem records at Edinburgh Royal Infirmary has shown that there has been no increase during 31 years in the incidence of intrathoracic neoplasm compared with total post-mortems, total tumours in all sites, total admissions or total deaths and that the rise noted in the last year or two is unlikely to be of any significance unless it continued and was sustained for several more years.

By contrast a definite increase in intrathoracic neoplasm is reported from at least 32 general hospitals out of a total of 43 in other parts of the world from which records are available. A detailed account, regarding the incidence of intrathoracic neoplasm in 42 general hospitals all over the world is contained in Bonser's\* paper published in 1934. Bonser, whose results are similar to mine discusses the subject at large and the following is more or less a resume of her work.

## (2) Incidence in Other Towns.

The difficulties which arise when the figures from different towns are compared are considerable, as there is not always any clear indication given as to whether all intrathoracic malignant new-growths are included or only those diagnosed as lung carcinoma. Similarly/

\*I am indebted to Dr. Bonser for reprints of her work.

Similarly the rate and extent of the increase reported by various authors cannot be accurately compared, as in some cases the figures are very incomplete and in others the total numbers are too small. These difficulties, however, are discussed very fully by Rosahn, Bonser and others and as an example of the difficulties encountered in assessing the value of the figures of two authors, Bonser quotes those of Kikuth (1925) for the Eppendorf Hospital in Hamburg and of Breckwoldt (1926) for the Barmbeck Hospital in the same town. (See Table IV).

TABLE IV. (Modified from Bonser).

Author.	Year.	% of P.M.s which were lung cancer.	Remarks..
Breckwoldt	1914-1917	0.46	No increase in 11-year period.
	1918-1921	0.14	
	1922-1925	0.52	
Kikuth	1914-1918	0.44	Doubling of % incidence in 10-year period.
	1919-1923	0.86	

Breckwoldt explains the apparent difference in his and Kikuth's figures for different hospitals in the same town by stating that the latter is dealing with larger numbers and therefore his results are probably more reliable. He did not suggest that there/



there might be local conditions which would determine an increase in lung cancer in one part of the town.

According to Rosahn for valid comparison of the incidence, definite criteria for diagnosis and statistical report should be established. Of these, he has modified the following from Weller:

- (1) An autopsy must have been performed;
- (2) The carcinomatous nature must have been verified microscopically;
- (3) There must be no reasonable doubt that the neoplasm was not a primary growth;
- (4) Percentage should be calculated on the basis of total adult necropsies.

According to Bonser the following points would facilitate comparison:

- (1) If it were known how many of the patients dying in hospital came to post-mortem examination, the part played by selection of material could be assessed. Rosahn (Boston City Hospital), Faulds (Glasgow Royal Infirmary), Duguid (Manchester Royal Infirmary) and Simpson (London Hospital) all state that some selection of cases for autopsy occurs in these hospitals.
- (2) A definition of the type of tumour included as intrathoracic or lung tumour is necessary.
- (3) The distribution of the sex of the cases throughout the year period should be given so that any difference in incidence between the sexes can be estimated.
- (4) Local conditions which might affect the numbers of respiratory tumours in a district should be mentioned.

Bonser in comparing the figures of British Hospitals/

Hospitals with those of other countries pointed out that the lowest figure in Britain is at St. Bartholomew's with 0.39 per cent of post-mortems in 1867-73, whereas in Germany a figure of 0.05 per cent was recorded from Göttingen in 1852-79. The highest figure in Britain is in Manchester, 3.28 per cent in 1921-5, whereas in Dresden 3.06 per cent occurred in 1926-30. Thus at the beginning of the century the Continental figures were of a lower order than the British ones and even though there has been such a marked increase in many towns, the continental and other country figures still do not reach such a high level as those in England and Scotland.

In Edinburgh the lowest figure 0.9 per cent was recorded for the period 1904-1908 and the highest was 1.9 per cent in the years 1929-33 (see Table II).

Thus to the above observation by Bonser and to which my findings add additional support Bonser says: "Can it be that the conditions affecting post-mortem statistics in other countries have not formerly been comparable with those in this country and that a change is now taking place, tending to bring them all into line, or can it be assumed that cancer of the lung is a more frequent occurrence in this country than abroad?"



ETIOLOGY.(1) Sex.

There is almost universal agreement that primary lung carcinoma is much more common in the male than in the female sex.

Of 95 cases (Group A.B.) 79 (83.1%) occurred in males and 16 (16.8%) in females. Accordingly, the proportion of male and female cases affected is approximately 5 to 1 and is thus in general agreement with those of other authors.

Of 209 cases (Group A.B.C.) which occurred between the years 1904-1934 inclusive, 168 occurred in males and 41 in females, the ratio being 4 to 1.

The following table is to record the findings of various authors. The slight difference which is noted between the results is mainly due to the number of cases examined by each author, as seen from the two different ratios recorded for Group A.B. and Group A.B.C.

TABLE V.

Author.	Total No.	Male.	Female.	Ratio.
Group A.B.	95	79	16	5:1
Group A.B.C.	209	168	41	4:1
Duguid.	175	151	24	63:1
Bonser.	170	132	38	35:1
Atkin.	93	80	13	6:1
Simpson.	139	111	28	4:1
Schuster.	62	46	16	3:1
Ormerod.	27	23	4	6:1



(2) Age.

Group A.B. consisted of 95 cases histologically proved to be primary bronchial carcinomata. Of the 95 cases 66 were oat-cell tumours and 28 were squamous, spheroidal and adenocarcinomata grouped together under the term obvious carcinomata.

TABLE VI.

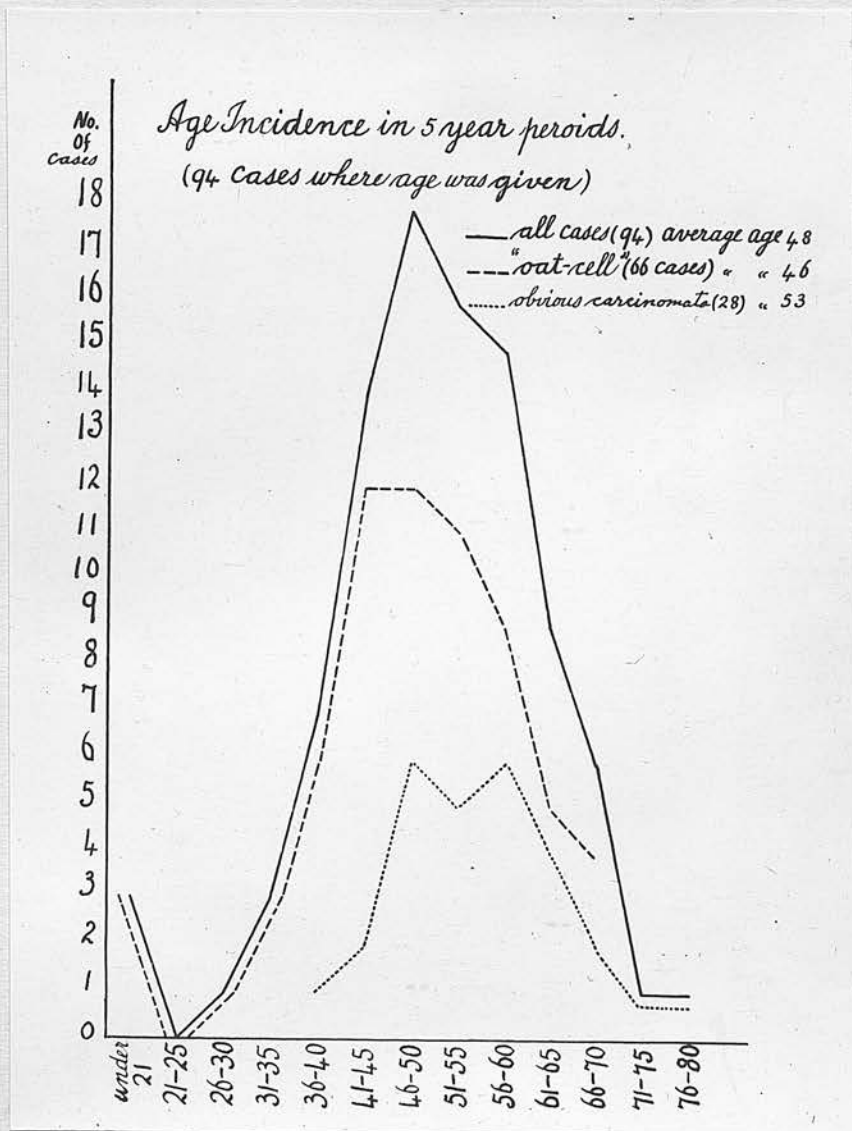
Age incidence (Group A.B.) in 94 cases where age was given.

Under	21		3
Between	21 and	25	0
	26 "	30	1
	31 "	35	3
	36 "	40	7
	41 "	45	14
	46 "	50	18
	51 "	55	16
	56 "	60	15
	61 "	65	9
	66 "	70	6
	71 "	75	1
	76 "	80	1

Average age 48 years.

In Table VI the age incidence is tabulated in 5-year periods. The highest incidence was between 41 and 65. The youngest patient was aged 18 and the oldest 76.

GRAPH/

GRAPH VII.

In Graph VII the average age of 66 oat-cell tumours was 46 and it is worthy of note that 7 cases occurred before the age of 36. The average age of 28 obvious carcinomata was 53 and it is to be noted that no case occurred before the age of 36. These figures are in agreement with those given by the majority/

majority of authors and support Barnard's opinion that the age incidence tends to be lower in the case of the oat-cell tumour.

In Barnard's series of 19 cases, 5 oat-cell tumours occurred before the age of 40 and the actual ages in the case of the obvious carcinomata varied from 44 to 61 and in the case of the oat-cell tumours from 27 to 66.

In Bonser's series, the average age of 59 oat-cell tumours was 46 and of these 8 cases occurred before the age of 30. The average age of 18 squamous was 55 years and of 48 other types of carcinoma 49 years.

In Simpson's series the youngest was 13 years of age and the oldest 77. The average age was 48 years and the majority of cases occurred between 40 and 68.

### (3) Occupation.

Of 95 cases constituting Group A.B. 79 were males and 16 females.

The 16 females were all housewives except one who was engaged as a ward-maid in the Royal Infirmary, Edinburgh.

Of 6 men there was no information as to their occupation. The remaining were:



- 11 miners
- 5 labourers
- 5 firemen
- 4 shopkeepers
- 3 motor drivers and chauffeurs
- 3 warehousemen
- 3 paper workers (stuffy atmosphere)
- 3 railway-guard-porters
- 2 piano-tuners
- 2 joiners
- 2 engineers
- 2 caretakers
- 2 barmen
- 2 schoolmasters
- 2 stud managers
- 1 commercial traveller
- 1 policeman
- 1 bank attendant
- 1 blacksmith
- 1 coach-smith
- 1 dentist
- 1 tailor
- 1 tobacco-pressman
- 1 electrician
- 1 ship's cook
- 1 retired ship-wright
- 1 ploughman
- 1 brewery worker
- 1 rubber-worker (exposed to great deal of dust  
and fumes of various chemicals)
- 1 house-painter
- 1 brush-maker
- 1 polisher
- 1 check-weigher in coal pit
- 1 quarry-worker
- 1 stone-mason
- 1 iron-moulder (inhales a great deal of iron dust)
- 1 chemical factory labourer

From the above list, none of these occupations would appear to be of any special etiological importance, excepting perhaps the quarry-worker, stone-mason, iron-moulder and the chemical factory labourer who was engaged in the manufacture of morphine, codeine, fusil-oil and exposed to lots of fumes/

fumes. Also the rubber worker who stated that he was exposed to great deal of dust and fumes of various chemicals.

Duguid traced the occupation in 143 of his male cases. Of these 29 were labourers, 9 carters and 8 clerks. In none of the other occupations were more than 4 cases recorded. Also, he found that the outdoor and indoor workers were in nearly equal proportion, there being 72 outdoor to 71 indoor workers. With the help of a census list from the Department of Public Health, Manchester, he was able to compare the percentage of tumour cases in the various occupations with the percentage of the whole male population of Manchester in these occupations, and as a result he judged that at least 75% of the adult population were indoor workers. Since, therefore, in the case of tumour there were actually more outdoor workers than indoor ones, he concluded that the incidence is higher in the former class in a proportion of 3 to 1.

Bonser (Leeds) in two of her papers which appeared in 1929 and 1934 respectively and from a study of the occupation in 144 male cases concluded that "there is no evidence in the figures to suggest that the occupation of the individual bears any relation/



relation to the incidence of the disease, a great variety of occupation being recorded. The numbers of indoor and outdoor workers are very nearly equal."

Schuster traced the occupation in 62 cases and concluded "No occupational association could be found, housewives, clerks, soldiers, mill-hands and labourers were equally represented."

Thus, from my own work and that of others there seems to be no relation between occupation and primary lung cancer. There is, however, one clear example of an occupational lung cancer. This is the Schnenberg miner's cancer and will be discussed under predisposing factors.

#### (4) Predisposing Factors.

##### (a) Trauma.

Of 95 cases (Group A.B.), 75 had reference to their previous history and of these 3 gave a history of traumatism as follows:

(Case No.9) 15 months before death a large stone fell on him and was crushed about the chest but no bones were broken and no spitting of blood after accident. Although the actual chest symptoms, did not start until 6 months before death, patient was getting pale and losing weight from the time of his accident.

(Case No.17) Received a bullet wound in right chest during the war but his chest symptoms only started 2 months before death in 1933. Right lung affected by tumour.

(Case/



(Case No.77) Accident in pit 4 years ago, involving left side of chest. Left lung affected by tumour.

Trauma has been considered a factor by some writers. Thus, in 1930, Wells and Cannon have reported an interesting case of primary carcinoma of the lung, arising in the periphery of the left upper lobe, at or about the site of a demonstrated traumatism to the lung, which produced haemoptysis and diffuse subcutaneous emphysema. Roentgenograms made the day after the traumatism, which showed fracture of the third, fourth and fifth ribs, gave no evidence of the existence of any neoplastic condition in the lung. Eleven months after the injury Roentgenograms showed a tumour in the periphery of the left upper lobe at the site of the trauma and death occurred  $23\frac{1}{2}$  months after the pulmonary traumatism.

In 1929, Knox in her review on Trauma and Tumours wrote: "A serious effort has never been made to ascribe pulmonary tumour to an injury. The case recorded by Lepine was that of a man who had sustained an injury to the chest wall and who one year later developed a squamous carcinoma of the lung beneath the site of the old injury. But serious injuries to the chest are so frequent and pulmonary tumours so rare that, statistically, a causal relationship is not/

not even suggested."

Weller (1929) quoted Aufrecht who considered severe trauma (which does not produce laceration of the pulmonary tissue, but only molecular disturbances of an unknown character) to be an important immediate cause of pulmonary carcinoma in 4 of his cases.

Lastly, it may be concluded that no matter what evidence of relationship of the trauma to the subsequent tumour may be presented, there is no possible way of proving that a symptomless tumour had not already been present at the time and at the site of the injury.

(b) Tuberculosis.

The prevailing opinion at the present time is that tuberculosis plays no part in the etiology of primary lung carcinoma, yet Ewing states that the chief etiological factor is tuberculosis. In support he quotes Wolf's series in which 13 of 31 cases were associated with tuberculosis.

In this series of 95 cases (Group A.B.) only 3 had evidence of tuberculosis. These were cases No. 32, 47 and 71. It would appear, therefore, that this infection does not predispose to carcinoma. In support of my findings I quote the following:

Of/



Of Adler's series of 374 cases 19 had evidence of tuberculosis. Kikuth in a series of 246 found tuberculosis mentioned in 22; Simpson, 6 of 139 cases; Davidson, 7 of a series of 107 and Schuster in her series of 62 found active tuberculosis in 2 cases.

Letulle in 1920 reported 2 cases of primary cancer of the lung developing in the vicinity of active tuberculosis and remarked that the condition was rarely encountered. I quote the following from his paper "Dans les deux, il s'agit d'un cancer primitif du poumon développé au voisinage de foyers bacillaires en évolution active, circonstance rarement réalisée, à en juger d'après mes nombreux protocoles d'autopsie."

Cherry in 1925 expressed the view that cancer attacks in later life those who have overcome the attacks of tubercle in early life. He considers that acquired resistance to tuberculosis is the predisposing cause of cancer, that the cells probably react in a different way to the same stimulus, the tubercle bacillus. He points out that the sum of the combined mortality rate for phthisis and cancer has varied very little for 30 years, constituting approximately 20% of all deaths after the age of 25.

Lastly, it may be concluded, as tuberculosis is almost universal and as a considerable number of individuals/



individuals have healed foci of infection either in the lungs or elsewhere, it seems unlikely that any close association should be formed between the two conditions.

(c) Syphilis.

Schmoller suggested this as a possible etiological factor.

In this series of 95 cases (Group A.B.) 4 had a positive Wassermann reaction without any obvious manifestation either in the lungs or aorta, and 2 had positive Wassermann reaction and showed evidence of syphilitic aortitis. Syphilis may, therefore, be excluded from having any etiological influence.

In Simpson's series of 139 cases 6 showed evidence of syphilitic lesions. Four showed syphilitic aortitis, of which 2 also had syphilitic fibrosis of the testicle. In the remaining two, one had syphilis of the lung, and the other had syphilis of the lung, liver and kidneys. Simpson remarked "In both cases the syphilitic and neoplastic changes occurred in the same area of the lung, although it is difficult to state on histological grounds that the one arose from the other."

Schuster in her series of 62 cases, found syphilis present in 3 cases, without any obvious manifestation/

manifestation in the lungs.

(d) Influenza.

According to Huguenin, Askanazy was the first to publish in 1918, the observation that there was a hyperplasia of the bronchial epithelium in many cases of individuals with influenza.

Ever since, it has been a favourite subject for theory on account of the special tendency in influenza for a chronic inflammation to persist with resulting fibrosis, bronchiectasis, epithelial hyperplasia and squamous metaplasia. In addition, the series of statistical publications emanating from Germany, U.S.A. and elsewhere called the attention to the remarkable increase in lung cancer and the suggestion was advanced that the bronchial epithelial hyperplasia which occurred in so many influenza cases was pre-cancerous and led to the development of cancer in susceptible individuals.

Among those who have supported this connection may be mentioned Grove and Kramer in America and Shennan in this country. Grove and Kramer quote Wohl (1922) who stated that the recent wave of pulmonary infections, such as streptococcic broncho-pneumonia and influenza, constituted an important factor in the formation of pulmonary neoplasms and they/



they remark "....., though the evidence is far from conclusive, it would seem more probable that acute inflammatory processes rather than chronic irritations play a strong role in enhancing the formation of neoplasms of the lung."

Shennan suggests that the increase in incidence during 1924 noted in his series of 22 cases, was the result of chronic interstitial pneumonia which remained as a legacy of the influenza epidemic 1918-1919; and in this connection Shennan wrote "The presence of old standing disease in at least 13 cases out of 22 primary cancers of the bronchus or lung cannot be ignored, and must be regarded as possibly influencing the onset of the new growth. The heavy incidence in the year 1924 may be accidental, but the evidence at least suggests that some attention should be paid to causes of chronic interstitial pneumonia. In this connection one may recall Adamis' insistence on the importance of the localisation of influenzal catarrh at the lower end of the trachea and in the main bronchi as opening up the way for invasion by streptococci and pneumococci which are responsible for what is called influenzal pneumonia. It is in this neighbourhood that many of these growths have originated. The chronic interstitial pneumonia may be/



be one of the legacies of the influenza epidemic of 1918-1919 which left so many of its victims with long persisting bad effects."

On the other hand many authors do not see any connection between influenza and bronchial carcinoma. Of these Hueper (1926) commenting on the connection wrote: "But their conclusions show many weak points and are in the final analysis not very convincing. First, we miss a similar sudden increase of lung carcinomas after the influenza epidemic in the years 1890 to 1894; second, the increase started in a minor degree already before 1920 as shown in the statistics of Stähelin and Hampeln; third, even the authors in favour of this theory could not prove the occurrence of a previous "influenza" a diagnosis which was quite misused at that time, in the majority of their cases (Läschke in less than 50%). Other investigators of the same question were unable to demonstrate this connection in a noteworthy percentage; fourth, the contrast in the male and female rates (Seyfarth 5.3:1, Berblinger 4.25:1) is an important objection against this theory."

Duguid of Manchester does not see any relationship between the two diseases and his observations are based on a large series of 175 cases. Kikuth found/

found reference to a preceding influenza in only 21 of 246 cases. In Schuster's series of 62 cases 6 gave a history of recent influenza with symptoms dating from that illness and 3 gave a remote history many years before, with complete recovery. In Simpson's series of 139 cases 5 had a history of influenza.

In support of those who do not see any connection between the two diseases is the fact mentioned by Kerely (1928): "Reykjavik, the capitol of Iceland, with a population of 22,000 suffered more from the influenza epidemic of 1918 than any other civilised community in the world. Despite this, pulmonary carcinoma is unknown there."

In this analysis of 95 cases (Group A.B.) 4 gave a history of having had influenza in 1918 and 4 gave a history of recent influenza with symptoms dating from that illness. In view of this and the fact that in Edinburgh there is no increase in lung cancer consequent upon the epidemic of influenza in 1918, it may, therefore, be concluded that the epithelial changes noted in influenza and described by Askanazy, Adami and others, may be considered favourable for the development of malignancy, but it is unwarrantable that any closer relation be alleged.

(e) Irritation by Inhalation.

1./



# 1. Experimental.

Since the positive results of the study in cancer production were demonstrated clearly by Fibiger with *Spiroptera neoplastica* and by Yamagiwa and Ichikawa with coal-tar, chronic irritation has been shown to be an important etiological factor in many types of cancer and it is natural that it should have been thought of in connection with the lungs.

Thus, in 1920, Winternitz, Smith and McNamara introduced dilute hydrochloric acid into the bronchial tree of experimental animals and were able to produce micro-photographs of what they described: "an over-production of the epithelium occurs and may form bronchiolar polypi or extend into the peribronchial tissue."

In 1923, Kimura was able to produce lung cancer by the intrabronchial insufflation of tar. The following is from his paper "By the intrabronchial insufflation is meant to force a small amount of crude coal-tar into the bronchus through the tracheotomy wound of the animals previously anaesthetised completely. Three rabbits and 10 guinea-pigs were used for this series of experiments. Among them, 1 rabbit and 3 guinea-pigs survived. After the treatment the former was killed on the 80th day and the/



the latter on the 140th day; there resulted a small adenomatous area in the lung of the rabbit and a multiple adenocarcinoma in one of the guinea-pigs." Kimura interpreted his results as adenocarcinoma of bronchial origin, produced by chemical stimulation alone, in an animal possessed of a special predisposition.

In 1925, Murphy and Sturm reported that tar-painting of the skin of mice sometimes produces lung tumours without skin tumours. It can occur in young animals which seldom have spontaneous lung cancer and can occur after painting the skin too short a time to produce skin cancer. The incidence ranged from 60.0% in one of their experiments to 78.3% in another. Control mice from the same stock but from 3 to 6 months older, and for that reason the more liable to spontaneous lung tumours, failed to show a single instance of such growths. Even in a stock in which spontaneous lung tumours had been frequent, the incidence for corresponding age periods has never been above 5.5% while the average has been between 1 and 2% over a period of years. Their explanation was that the lung tumour was caused not by the direct action of the tar but that the tar lowered the resistance of the animals, so that they became susceptible to the irritation/

irritation of inspired sawdust "Our mice lived in burrows under sawdust and shavings mixed with chopped hay. There is every probability that the inhalation of some small foreign particles resulted in irritation." It was believed that the inhalation of particles of tar could be ruled out as a cause.

However, in 1934 Argyll Campbell, subjected mice to repeated exposures to dust obtained by sweepings from tarred roads and containing about 2% of tar. Cancer of the skin developed in 70% of those surviving long enough. The incidence of primary adenoma of the lung was increased to tenfold that of the controls. Commenting on the work previously done by Murphy and Sturm in 1925, he wrote: "Murphy and Sturm's result has a distinct resemblance to that of the present research. They thought that the tar-painting reduced the general resistance to cell growth, and that inhalation of some small foreign particles other than the tar resulted in the irritation of the lung so that tumours developed. They did not think that the tar could become particulate, but the present research indicates that the carcinogenic agent does get into a dust cloud perhaps by being adsorbed on other dust particles." In conclusion he said "The bearing of this research upon the debated increase in tumours of the/



the human lung cannot be assessed at present. The mice were exposed to much more excessive dusting than occurs with human individuals. Cleanliness prevents cancer of the skin in man, and the natural mechanism for removal of dusts from the healthy lung may suffice for the small amounts of dust inhaled. There is the further question whether these tumours of mice may be compared with those of the human lung."

From this survey it may be seen that some success has been obtained in producing tumour-like structures in the lungs of laboratory animals particularly mice and that tar and tar derivatives have been the most successful aids in bringing this about.

Returning to a consideration of the etiology of carcinoma of the lung in man, one finds that a great variety of irritative agents have been suggested. Among those which are now generally discredited may be mentioned tobacco smoke and the poison gasses used during the war. In this analysis of 95 cases (Group A.B.) 5 had a history of excessive smoking and there was no reference to any gassing during the war in the entire series of 95 cases and only one case gave a history of having been gassed in 1918 and ever since had had bronchitis on and off with/



with copious sputum. This was Case No.104 and the only one met with in Group A.B.C. which consisted of 212 cases.

## 2. Clinical.

The clinical aspect of the development of carcinoma of the lung is exemplified by the "Schneeberger Lungenkrebs" in Saxony and this being the only one definite example of its kind, it merits a full discussion.

According to Rostoski, Saupe and Schmorl, it has been known since the beginning of the 16th century that the miners in that particular mine suffered from a disease of the lungs of which they usually died toward the middle years of life: "Seit mehreren Jahrhunderten ist unter den Bergleuten des sächsischen Erzgebirges ein Lungenleiden unter dem Namen Bergkrankheit, Berg-oder Lungensucht bekannt, das meist in mittleren Lebensalter zum Tode führt. Gute, zum Teil sogar treffliche Beschreibungen finden sich schon in alten Chroniken und Berichten von Agricola (1500), Matthesius (1559), Pansa (1614), Engelschall (1723), Henckel (1728), Scheffler (1770), Küchenmeister (1869) u.a."

In 1879, it was recognised by Härtling and Hesse that/

that this peculiar affection was a malignant tumour. They stated that a lymphosarcoma of the bronchial lymph nodes or an endothelial sarcoma was responsible for 79% of all the deaths among the miners of the Schneeberg district in Saxony. In addition, they supposed that the etiological factor was the arsenic contained in the mineral dust. The dust inhaled in the mine is composed of  $\text{FeS}_2$ ,  $\text{CoAs}_2$  and  $\text{NiAs}_2$ . It has a high arsenic content and microscopic examination shows the metallic particles in it to be particularly sharp. Small amounts of uranium and of other radioactive minerals are also present. Besides, various small fungi grow in profusion in the mine.

Recently Rostoski, Saupe and Schmorl carried out thorough clinical and pathological investigations over a period of 3 years. They made observations on the 154 miners and on 362 people of the same district not engaged in mining. During the 3 years 21 miners died. In 13 an autopsy was done and all had carcinoma of the lung as well as pneumoconiosis. Of the 8 upon whom no autopsy was done 2 had been diagnosed clinically as having carcinoma of the lung. The average age of these men was 55 years and the average period of working in the mines was 25 years, with a minimum of 10 and a maximum of 45 years. Two other men/



men who died of lung cancer had worked in the mines for 10 and 17 years, respectively, but had left the mines 15 and 22 years before death. No cancer was diagnosed in the 362 people of the same district not engaged in mining. Nine cases originated in the large bronchi and 6 in the lung tissue and all were carcinomas. They suggested as possible carcinogenic agents the arsenic content of the dust (up to 0,5%), the radium emanation content of the air, and possibly the frequent colds from which the miners suffer. They said that occupational cancer of the lung has not been discovered in other miners, but they suggested its possible occurrence in the Joachimstal mines in Czecho-Slovakia, where hitherto the lung affections of the miners have been diagnosed as tuberculosis.

In 1930, Šikl published a report of occupational lung cancer in the pitchblende miners in Joachimstal, Czecho-Slovakia. The mines have been worked since 1516 and have yielded silver, cobalt, nickel, bismuth and arsenic and pitchblende since the discovery of radium by Madame Curie at the beginning of this century. The miners number about 320, of whom 80 are retired. Until 1921, no particular frequency of lung cancer was observed but in 1929 Löwy described autopsies on 10 miners (of 15 who died prior to 1930) and/



and stated that cancer of the lung or pleura was found in 8 cases. The average age was 48 years and the duration of work in the mines varied from 13 to 33 years.

It was mentioned above that 13 cases were autopsied by Schmorl and that all had carcinoma of the lung as well as pneumoconiosis. Therefore, the contrast between the associations of silicosis and tuberculosis in S.Africa and silicosis and cancer in Saxony is of interest. In the Schneeberg mines tuberculosis is relatively rare, while in Africa tuberculosis is the commonest complication of silicosis. On the other hand the figures from the S.African mines, according to Simpson, show that "Carcinoma of the lung is a rare complication only occurring together with silicosis in 2 cases during the years 1924 to 1926. Apart from silicosis it occurred in 5 cases during that period."

One may, therefore, conclude that silicosis is not in itself a vital factor in predisposition to lung cancer and that the prevalence of lung cancer in Schneeberg must be due to some other factor, possibly due to the radio-active minerals present in those mines (Schneeberg and Joachimstal mines). However, one must not forget that heredity may play some/

some role in the etiology since the work has been in the hands of a few families for many generations. This will lead us to the last chapter in etiology, namely heredity.

(f) Heredity.

Weller in 1929, under intrinsic predisposition wrote: "Most writers on the subject dismiss with a brief negation the possibility that an inherited predisposition is of importance in the etiology of carcinoma of the lung. That this should not have received fuller consideration is all the more remarkable since the tumours of the lung in mice have played an important part in the experimental proof of the importance of hereditary factors as this has been developed by the work of Slye, Tyzzer, Lynch and others ..... with this important lead, it is surprising that the reports of cases and the statistical studies of carcinoma of the human lung practically never mention a family history of malignant conditions whether it be negative or positive."

In this analysis of 95 cases (Group A.B.) 20 had no reference to their family history. In the remaining 75 cases, 7 gave a positive history as follows:

Case/

Case No.1. Mother died aged 63 years from "tumour of gullet" and one brother died aged 43 from "cancer in throat".

Case No.40. One brother died aged 60 of "tumour of spine".

Case No.48. Two brothers died of gastric carcinoma.

Case No.68. Mother died of "cancer of liver".

Case No.76. Father died of "cancer of stomach".

Case No.83. Father died of "tumour of liver".

Case No.93. Father died aged 64 from "gastric carcinoma".

But the predominance of a negative history, the unreliability of many personal and family histories and the difficulty of applying experimental selective breeding experiments in animals to man, make such a factor too vague and inconclusive.



PATHOLOGY.(1) Situation in the lung.

It is generally stated that cancer of the lung is more common on the right side than on the left. Some authorities suggest that there may be some relationship between this preponderance and the anatomy of the right bronchus which is wider than the left in the proportion of 100 to 78.4 and it has a more vertical course. It therefore lies more in the line of the trachea and to this, as well as to its greater width is due the greater tendency which foreign bodies exhibit when introduced into the trachea, to drop into the right bronchus in preference to the left.

In Group A of my series both lungs were equally affected and in Group A.B. the left lung was more affected than the right and still in Group A.B.C. both lungs were more or less equally affected if we considered the fact that in this group 16 cases were reported as involving both lungs and 4 cases with incomplete post-mortem notes (see Table VII).

As a matter of fact, one finds that some authors report it more common on the right and others on the left side as can be seen from Table VII which is drawn up to demonstrate more plainly the findings of various/

various authors.

TABLE VII.  
Site of Growth.

Author	Total No. of cases	Right lung	Left lung	Both lungs	Not stated	Authors' opinion.
Group A	38	18	18			Both sides are equally liable to be affected.
" A.B.	95	44	45	5	1	
" A.B.C.	209	101	88	16	4	
Kikuth	246	123	118	5		
Maxwell	184	93	90		1	
Simpson	139	69	70			
Atkin	93	52	41			
Ferenczy and Matolocsy	236	144	92			A preponderance in favour of right side.
Wahl	81	49	28	4		
Schuster	57	31	23	5		
Hanf. D.	167	72	95			A preponderance in favour of left side.
Probst	76	36	40			
Tudor Edwards	73	33	40			

In view of this conflicting evidence and my personal findings, it does not seem probable that there is any etiological significance in the situation of the tumour. Also, as the fumes and minute dust particles are very freely disseminated, it can hardly make much difference in its effect on the two lungs.

As regards the actual site of origin, also this has been tabulated (see Table VIII). It is the main

TABLE/



TABLE VIII.

Author.	Total No. of cases	Right lung				Left lung			No bronchial involve- ment.	Both lungs	Not stated
		Main bron.	Upper bron.	Middle bron.	Lower bron.	Main bron.	Upper bron.	Lower bron.			
Group A	38	11	5	1	1	15	1	2	2*		
" A.B	95	27	9	3	2	32	7	6		5	1
Maxwell	184	54	21	2	16	59	15	16			

\*These 2 cases are No.37 and 38 and are discussed under Histogenesis.

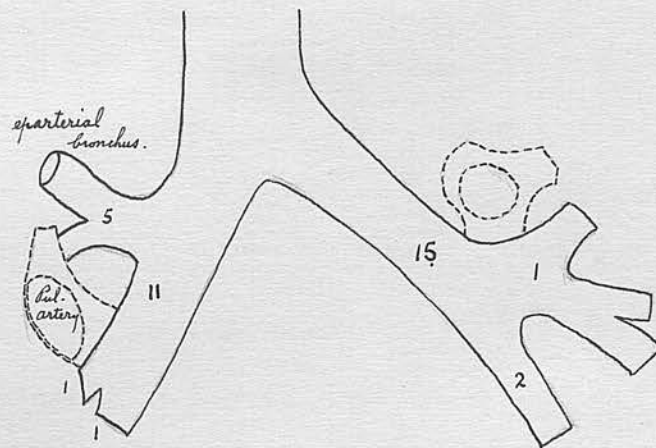
bronchus or the main branches to the lobes (particularly the upper lobe branch) which in the majority of cases are responsible for the growth.

In Group A which included 38 cases, the actual site of origin was clearly demonstrated in 36 cases and this was mainly situated in the distal part of a main bronchus or the proximal part of a main branch. The finding is in agreement with most authors.

From the following diagram it can be learned that the angle formed by the eparterial and the main bronchus is a favoured situation for the development of carcinoma. It is to be remembered that the eparterial bronchus arises nearer the trachea than the first branch of the left bronchus.







## (2) Gross Morbid Anatomy.

**Technique.** - Most of the post-mortems which occurred in the years 1933 and 1934 were performed by myself. After the routine examination of the case in the post-mortem room, the lungs and the organs containing metastases were sent to the University where they were fixed in Kaiserlings solution and then studied carefully. All the bronchi were exposed in search of the primary site. The lung was photographed and then cut into several sections about 0.5 cm. thick. Those cases which appeared worthy of keeping were then mounted. Organs with metastases also were carefully examined.

The gross appearances of 38 cases will be considered which include the following microscopic varieties/

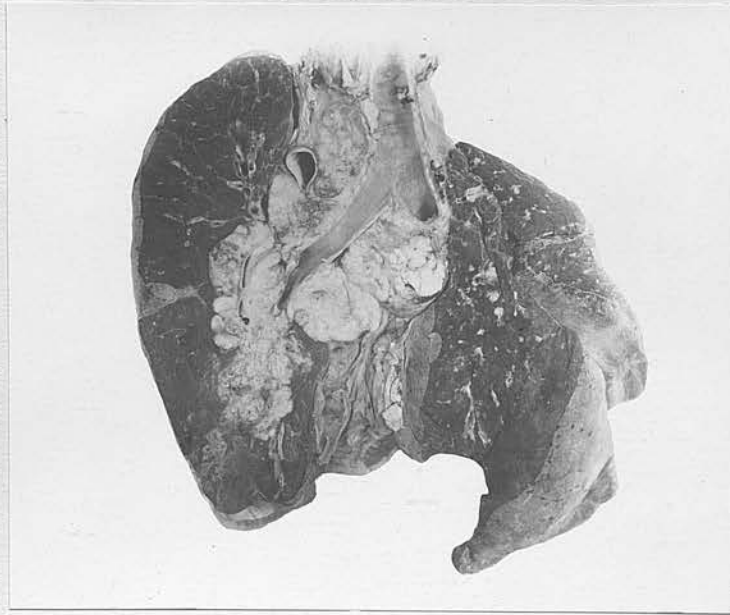
varieties: 1 spheroidal cell, 3 squamous, 5 adenocarcinomata and 29 oat-cell tumours. When necessary the first 3 varieties are considered under the term "obvious group". Of these, 3 cases are not discussed in this section. These are Nos.18, 37 and 38. The former case is described under the section of mode of spread and the latter two cases are discussed under the section of Histogenesis.

The macroscopic appearances of bronchial carcinoma present a fairly wide range of variety according to the size of the growth, the mode of spread, the complications and the changes which have occurred in the main mass of the tumour by reason of secondary degenerative processes. However, the majority of cases are fairly characteristic.

In most cases there was a mass of growth surrounding a large bronchus and situated usually near the hilum. The lymphatic glands were either very large and discrete or else had become matted together to form a large mass or masses filling the mediastina. (See Plate II). The consistency of

PLATE/



PLATE II.

the growth was generally firm and the cut surface was homogenous greyish-white with soft yellowish areas of necrosis scattered throughout. In some of the tumours degeneration and necrosis had occurred, while in others purulent inflammation and small haemorrhages had complicated the naked-eye appearance. It was impossible to distinguish macroscopically the oat-celled tumours from the obvious carcinomata. The masses in the lungs were not appreciably larger in the one group of cases than in the other, neither was the proportion of mass in lung to mass in glands constantly different in the two groups. They all had certain features in common, namely bronchial obstruction/

obstruction, mediastinal involvement and distant metastases.

Barnard, in his classical paper distinguished the squamous bronchial carcinoma from the other types as being hard, with coarsely granular milky-white cut surface and a large mass extending from the hilum of one lung and replacing the greater part of its substance. The lymphatic glands as comparatively small and discrete and with no evidence of spread to other structures. Whereas the obvious carcinomata other than the squamous-celled and the oat-celled tumours as being identical in that they tend to be softer and produce a large mass in the mediastinum and a small mass in the hilum of one lung.

This distinction between the squamous and the other carcinomata was not confirmed in this series as seen in Cases No.11 and 16. Both cases were squamous-celled and both showed a small mass in the hilum of one lung and a larger mass occupying the mediastina and in both wide-spread metastases had occurred which affected pancreas, liver, suprarenal and kidney. In fact the oat-cell tumour may remain confined to the lung whilst the most fully differentiated squamous or adeno-carcinoma may become widely disseminated.

This/

This inability to recognise macroscopically the various microscopic varieties of bronchial carcinoma is agreed upon by most authors. The following Table IX is to record some of the statements made by the various authors on the subject.

TABLE IX.

Author.	Author's Quotation.
Barnard	"Setting aside the squamous-celled carcinomata, there is no essential difference in macroscopic appearances or distribution between obvious carcinomata and oat-celled tumours, both the part of the lung affected and the metastases being exactly similar in many cases."
Bonser	"Even after examining a large number it has not been possible to foretell with any degree of accuracy the nature of the tumour from its naked-eye appearance."
Schuster	The small cell tumours. "They have the same gross characteristics as the other groups; some have a mass in the lung and some but not all, a mass in the mediastinum."
Simpson	"Macroscopically the oat-cell tumours may be indistinguishable from a typical carcinoma."

Lastly, some authors such as Maxwell and Huguenin have tried to classify cancer of the lung upon/



upon the basis of gross morbid anatomy. But, these classifications have been largely abandoned and rightly so, because of wide variations in form, which overlap the classes, apparently as the result of local extensions and regional metastases.

### (3) Mode of Spread and Metastases.

The study of the gross and microscopic features in 38 cases of bronchial carcinoma has demonstrated many of the numerous methods by which cancer of the lung may spread. These may be divided into:

- (a) Direct extension.
- (b) Lymphatic spread, usually local.
- (c) Blood spread, usually distant.
- (d) Aspiration.

#### (a) Direct Extension.

(1) Direct extension may occur along the surface of the mucosa. To some extent this was noted practically in every case where the site of origin was clearly demonstrated particularly in the larger bronchi. The mucosa in the neighbourhood of the primary site being replaced by whitish tumour tissue. In more than one case the growth has spread to involve and replace the mucosa of the lower part of the trachea and the proximal part of the opposite bronchus.

But/

But in the majority of cases this spread was in a peripheral direction with replacement of the bronchial epithelium by tumour cells along the lines of the bronchial tree. Cases No.18 and 26 afford good examples, in which no pulmonary growth was evident until the bronchi were opened.

Similarly extension may occur round the circumference and produce partial or complete occlusion of the lumen. This was noted in 26 cases.

In some cases the growth was seen shining through the raised and thinned out but intact mucosa. This was confirmed microscopically by the surface epithelium being intact.

(ii) Direct extension also occurs in the substance of the lungs and thence to the surrounding tissues, the pleura and mediastinum. The interlobar, interlobular septa and alveolar walls are used as a support. In the majority of cases pleural and mediastinal involvement were due to lymphatic spread which is discussed below.

(b) Lymphatic spread, usually local.

The lymph vascular system is a common route along which malignant disease is conveyed either as emboli/



emboli or by permeation. Before discussing this mode of spread a brief resume (from Maximow Test-Book of Histology) may be made of the lymphatic system of the lung.

"There are two main divisions of the lymphatics of the lungs. One set is in the pleura and the other in the pulmonary tissue; these two sets communicate very infrequently; both of them drain into the lymph nodes at the hilum of the lung. The lymphatics of the pleura form a dense network with large and small polygonal meshes. The large meshes are surrounded by large vessels and demark the lobules; the small meshwork is formed of smaller vessels which mark out the anatomical unit (the unit begins with the respiratory bronchiole and extends to and includes the alveoli). There are many valves in these lymphatics which control the flow of lymph so that it passes to the hilum and not into the pulmonary tissue. These pleural lymphatics combine into several main trunks which drain into the lymph nodes at the hilum.

The pulmonary lymphatics may be divided into several groups which include those of the bronchi, of the pulmonary artery and of the pulmonary vein. The lymphatics of the bronchi form an anastomosing network in the wall of these tubes. They terminate in/



in the alveolar ducts and their end branches join the lymphatic radicles of the plexuses about the pulmonary artery and vein. There are no lymphatic vessels beyond the alveolar ducts. The pulmonary artery is accompanied and drained by two or three main lymphatic trunks. The lymphatics associated with the pulmonary vein begin with its radicles in the alveolar ducts and in the pleura. All of the lymphatics of the pulmonary tissue drain towards the hilus nodes. There are no valves in the intrapulmonic lymphatics except in a few vessels, in the interlobular connective tissue near the pleura, which accompany the branches of the pulmonary veins. These lymphatic vessels connect the pulmonary and pleural lymphatic plexuses. As their valves point only toward the pleura, they provide a mechanism whereby lymph can flow from the pulmonary tissue into the pleural lymphatics if the normal flow of lymph in the former towards the hilum is interrupted."

Involvement of the pulmonic set of lymphatics was clearly seen macroscopically in the majority of cases and microscopically in every case. There occurred radiating processes from the main growth at the hilum along the bronchi and vessels (see Plate/



Plates III and IV). In addition the regional glands (bronchial and mediastinal) were affected in 32 cases.

PLATE III.



PLATE IV.

"oat-cell" peribronchial lymphatic spread.





The pleura in 7 cases showed nodules of malignant growth. In 5 of these 7 cases direct lymphatic spread from the tumour at the hilum to the pleura was visible. In the remaining 2 cases no connection was seen between the primary growth in the hilum and the secondaries in the pleura. This was either due to retrograde lymphatic embolism or to involvement by way of the blood stream.

In three cases, widespread lymphatic permeation gave the lung a different appearance from that usually seen in bronchial carcinoma.

PLATE V.

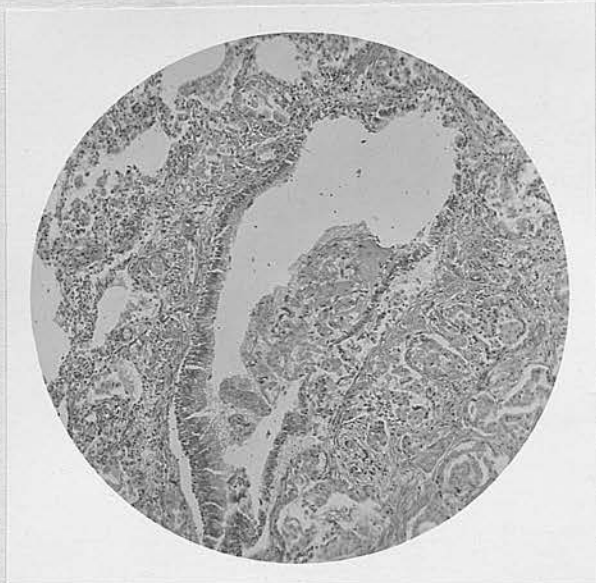




The first of these was Case No.18 (Plate V) in which the right lung failed to undergo the usual degree of collapse but remained semi-distended on the table. The pleura exhibited some fibrous thickening and the lobes were loosely held together by fibrous bands. The lung substance was fairly tough. Section revealed a reddish brown surface throughout which coursed numerous fibrous bands of varying thickness which macroscopically suggested fibrous results of pneumonic processes. Nothing pointing to tumour. The primary in a medium sized bronchus in the upper lobe was rather inconspicuous and was only revealed when whole sections were taken for microscopic examination. Microscopically, there was widespread peribronchial, perivascular and pleural lymphatic permeation and those white bands seen naked-eye were in reality lymphatic vessels distended with columnar cells. Many bronchioles showed masses of tumour cells lying free in the lumen amongst desquamated columnar epithelium. In one or two areas the growth was seen, spreading from the peri-bronchial lymphatics, making a hole in the lining mucous membrane and protruding into the lumen of the bronchiole (see Plate VI). The alveoli surrounding most of the bronchioles were lined and

PLATE VI.

"Adeno-Carcinoma" Peri-bronchial lymphatic spread and protrusion of growth into lumen.



filled with tumour cells giving a microscopic appearance of what may be termed malignant broncho-pneumonia. The interesting features of this case are the absence of metastases in the regional glands and the fact that the diagnosis could only be made with the aid of the microscope. A similar case was described by Morelli in 1907 and quoted by Adler.

The other 2 cases presented to the naked-eye the typical appearances of grey consolidation seen in lobar pneumonia. In both widespread lymphatic permeation was present with absence of involvement of the regional glands. These 2 cases are remarkable for/



for other important features and are discussed in other connections (see Histogenesis).

(C) Blood Spread, usually distant.

The blood stream affords a ready means by which malignant emboli may be widely disseminated.

Ulceration into a radicle of a pulmonary vein or arteriole was noted in the majority of cases, even in cases where there were no macroscopic metastases, e.g. Case No.20 (see Plate VII and VIII). Or malignant cells may reach the right auricle via the broncho-mediastinal and thoracic ducts and as a result metastatic nodules may be produced into the lungs such as was the case in Case No.11.

PLATE VII (x 60) Invasion of small artery by squamous-celled-carcinoma. Note malignant cells in lumen.

PLATE VIII (x 350) Higher magnification of area marked by ☐ in Plate VII. Note malignant cells between the elastic fibres.

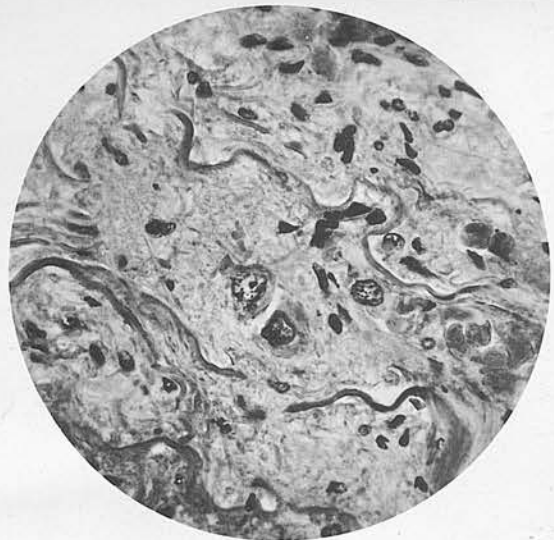


PLATE IX. (x 45) oat-cell invasion of small artery.

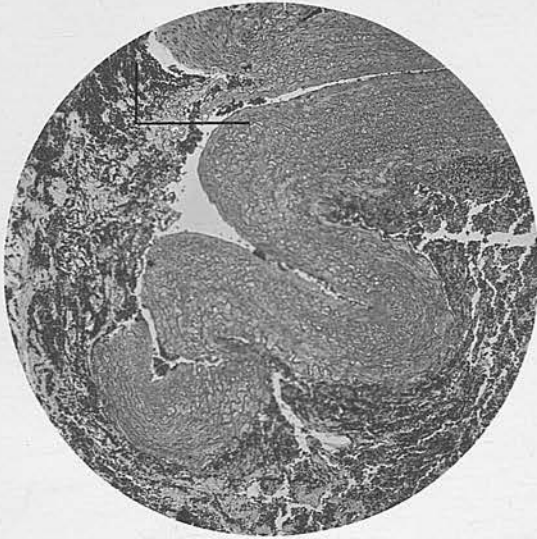
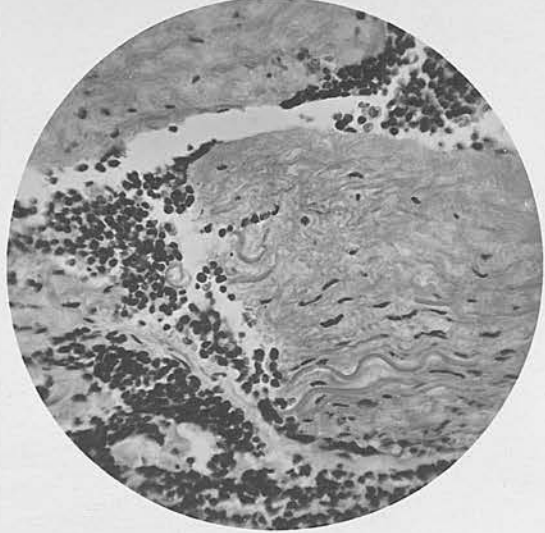


PLATE X. (x 240) Higher magnification of area marked □ in Plate IX.



Spread by means of the blood system may occur at any stage in the course of the process and may result in few or multiple metastases.

In this series of 38 cases, the liver was the commonest site of secondary growth. It was affected in 12 cases (31.5%). The metastatic nodules varied greatly in size in different and same cases, but all were more or less round and discrete except when they had coalesced. In other words, the appearances were typical of involvement by way of the blood stream. Neither direct spread to the liver nor lymphatic spread via the lymph-vessels through the diaphragm or from/

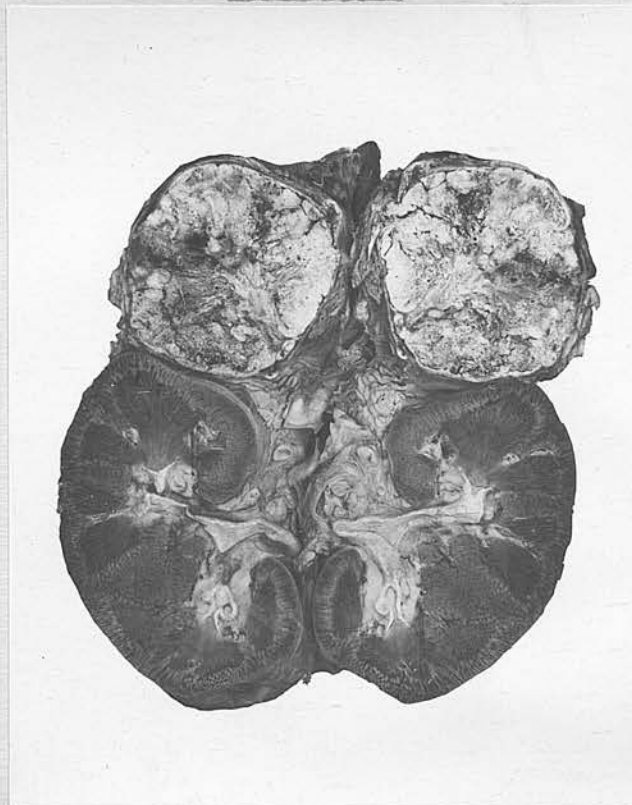


from the coeliac glands did occur in this series. Next in order of frequency were the suprarenal glands. They were affected in 9 cases (23.6%).

The embolus of tumour tissue is usually embedded in the medulla of the suprarenal and as it grows bigger it stretches the cortex of the gland.

The size of the nodule varied in different cases from that of a marble to almost the size of the kidney itself (see Plate XI). The importance of this lies in the fact that the case may be mistaken macroscopically for a primary suprarenal tumour as occurred in case No.11. In 4 cases both suprarenals were affected and in the remaining 5 cases only one suprarenal was affected.

PLATE XI.



Secondary growths in the pancreas were noted in 9 cases (23.6%). Here, sometimes it was difficult to distinguish between blood spread and direct spread from adjacent glands. However, in the majority of cases several rounded nodules were discovered scattered throughout the organ indicative of blood spread.

Next in frequency were the kidneys. They were affected in 6 cases (15.7%).

The brain was affected in 5 cases (13.1%). It is certainly affected more often than is supposed as it is not always examined at autopsy and probably the percentage is much higher than this. The importance of intracranial metastasis lies in the fact that of the organs involved the brain is often the only source to which symptoms are referable. Cerebral metastasis is due to blood spread. Of the 5 cases, 3 involved both cerebrum and cerebellum and 2 the cerebrum only.

In this series no spinal cord metastases were found and the cases which presented spinal cord symptoms were the result of pressure from metastasis in the vertebrae, e.g. Case 19.

Bones were affected in 3 cases (7.8%). Again, they were not always examined at autopsy and when so, they were examined most inadequately, the shaft of the femur being the only bone examined. Accordingly the percentage/



percentage must be much higher than this. The individual bones were: Case No.19, vertebrae only; Case No.29, skull only; Case No.2, vertebrae, sternum, ribs, iliac and femur. Even from these 3 cases it can be seen that it is not always the femur that should only be examined. These secondary growths were all due to blood spread, though it should be remembered that the vertebrae may be affected by retrograde dissemination through the lymphatics.

Thus, the skeletal system as well as the central nervous system are favoured sites for metastases in bronchial carcinoma. Also, the importance of bone metastasis lies in the fact that the primary symptom may be a pathological fracture as seen in Case 139. Or the bone metastasis may be mistaken for a rare primary carcinoma of the bone as seen from the literature. Powell White and G.E. Brunton in 1927, placed on record a series of uncommon tumours which had come under their notice. Their case No.5 of primary carcinoma of femur might have been a secondary from a primary lung carcinoma. They described a necrotic nodule in the lower lobe of the left lung and microscopically the growth was a typical columnar-celled carcinoma both in the alleged primary focus in the femur, in the iliac glands and in the lung.

(D) Aspiration.

Aspiration of tumour fragments via the bronchi may play a part in the dissemination of tumours from one part of the lung to another or to the opposite lung.

This was clearly seen in Case No.18 in which this mode of spread must account to a certain extent for what was termed microscopically malignant broncho-pneumonia (see p.63). Thus in this case and probably in many others aspiration has contributed to the dissemination of tumour cells from one part of the lung to another.

Case No.37 is a probable example of dissemination by aspiration into the opposite right lung. Left lung was uniformly consolidated. Macroscopically it was grey in colour and had the features of grey consolidation typical of lobar pneumonia. The right lung showed small tumour nodules, ranging from 1 to 3 m.m. in diameter, mostly related to the bronchioles, scattered throughout its substance and not particularly numerous underneath the pleura. The pleura was smooth, glistening and free of tumour nodules. The bronchial and mediastinal glands were neither enlarged nor involved by tumour tissue. The bronchi were free of growth and there were no other metastases.

The/



The following Table indicates the frequency with which various parts of the body are affected in the various groups studied.

TABLE X.

Organ.	Group A.						Group A.B.						Group A.B.C.	
	Oat-cell & obvious		Oat-cell alone.		Obvious alone		Oat-cell & obvious		Oat-cell alone		Obvious alone		Oat-cell & obvious	
	38 cases		29 cases		9 cases		95 cases		66 cases		29 cases		209 cases	
	Case	%	Case	%	Case	%	Case	%	Case	%	Case	%	Case	%
Regional glands	32	84	26	89	6	66	84	88	64	96	20	68	197	94
Abdominal glands	4		4				18	18	13	19	5	17	31	14
Cervical glands	5		5				13	13	12	18	1	3	24	11
Liver	12	31	10	34	2	22	35	36	27	40	8	27	65	31
Supra-renal	9	23	6	20	3	33	19	20	15	22	4	13	35	16
Pancreas	9	23	8	27	1	9.9	18	18	16	24	2	6	30	14
Kidneys	6	15	5	17	1	9.9	16	16	11	16	5	17	30	14
Brain	5	13	5	17			8	8	8	12			15	7
Bones	3	7	3	10			11	11	9	13	2	6	25	11.9
Spleen	1		1				3	3	3	4			7*	3.3
Peritoneum	1		1				1	1	1	1.5				
Other lung	1						10	10	4	6	6	26	22	10
Gall-bladder							2	2	1	1.5	1	3.4	3	1.4
Thyroid							1	1	1	1.5			2	.9
Ovaries													1	.4
No metastases	5	13.1	3	10.3	2	22.2	7	7.3	3	4.5	4	13.7		

\*The occurrence of 7 cases in which there were metastases in the spleen calls for comment in view of the fact that it is often difficult to differentiate intrathoracic cancer from lymphadenoma especially when the disease is far advanced and that involvement of the spleen is much more common in Lymphadenoma than in the case of malignant disease. Three of these 7 cases were confirmed histologically and in the other 4 cases the description was so accurate as to exclude any doubt as to its nature. Also the spleen was described as to contain only one nodule of malignant tissue.

Conclusions from above Table X are:

1. The obvious carcinomata have a rather less tendency to metastasise than the oat-cell tumours and that absence of secondary growths occurs both in the obvious and the oat-cell tumours.
2. The regional glands are invaded in the majority of cases by both types of tumours, but the extra-thoracic glands are more often invaded by the oat-cell tumour than by the obvious carcinoma.
3. Brain metastases and most of the skeletal metastases are usually due to the oat-cell tumour and that the brain and skeletal system are favoured sites for metastases in bronchial carcinoma.
4. Of the viscera, the liver is the commonest site of metastases. Next in order of frequency are the suprarenals which are frequently invaded by both types of tumours.

Table XI has been compiled to compare my own results with those of other authors.

TABLE/



TABLE XI.

Author	Total No. of cases	Regio- nal glands	Liver	Supra- renals	Panc- reas	Kid- ney	Brain	Bones	Spleen	Peri- ton- eum	Other lung	Gall- blad- der	Thy- roid	Ova- ry
Group A. B.	95	84	35	19	18	16	8	11	3	1	10	2	1	1
" A. B. C.	209	197	65	35	30	30	15	25	7	1	22	3	2	1
Adler**	374	229	103	38	6	58	28	48	18	7	43	1	12	1
Kikuth	246		70	21	11	25	31	8	2	10		1	5	1
Maxwell	184	134	60	32	21	29	16	8	5					2
Duguid	175		27	18		9	2	8	1			1	1	
Bonser**	172		43	26	15	27	7	7	3				1	3
Simpson**	139	104	45	41	25	14	19	13	5	12	16		4	
Wahl	81	60	26	18	8	15	7			1	22		11	5
Schuster***	57													
Grove & Kramer	21	18	12	5	4	8	5	8	2	2			1	
Rist & Rolland	11	8	5	1		2		2	1					

\*Note that Adler published 374 cases carcinomata and 90 sarcomata. These figures are certainly inaccurate for undoubtedly many of the oat-cell carcinomata were included amongst the sarcomata.

\*\*Simpson did not give the total number of cases with secondaries in the skeletal system. He only mentioned the frequency of affection in the individual bones and as more than one bone may be affected in the same case, his results cannot be recorded in this table. The bones affected in his series were: vertebrae, 29; femur, 21; ribs, 15; sternum, 8; skull, 5; pelvic bones, 4; humerus, 2; clavicle, 1. Total of these is 85, but as pointed above this figure does not mean the number of cases with skeletal metastases.

\*\*\*Schuster did not give the total number of each organ affected, but spoke of the metastases in a general way. I quote the following from her paper as her results agree with my findings:

"The liver is the commonest site after the cervical glands, and the suprarenal is a favoured spot. The histological structure is quite indiscriminate, and there does not seem to be any predilection of a special type of growth for special organs, except the brain, where they were nearly always small cell tumours."

#### (4) Pathological Complications of Group A.

The growth itself may undergo:

##### 1. Degeneration.

This was seen most commonly as small soft yellowish areas scattered throughout the growth but in few cases it was rather massive.

##### 2. Purulent Infiltration and Abscess Formation.

These were noted particularly in cases with advanced bronchial obstruction and bronchiectasis.

##### 3. Haemorrhage.

This was a rare occurrence and was met with in the form of pin-point haemorrhages.

#### Pleura.

Pleural effusions occurred in 22 cases of which 1 was sanguinous, 8 clear and 13 purulent (empyemata). Malignant infiltration of the pleura occurred in 7 cases. Chronic fibrous adhesions occurred in 17 cases. Thus it is seen that the pleura is involved in one form or another in the majority of cases.

#### Lungs.

Bronchitis, broncho-pneumonia, bronchiectasis, collapse, gangrene, abscess formation and fibrosis may all occur. A certain amount of bronchitis was present in every case. Broncho-pneumonia occurred in



12; bronchiectasis, 22 (in one case pulmonary osteoarthropathy was noted); collapse, 10; gangrene, 4; abscess formation, 2; and fibrosis, 3 cases.

Partial or complete occlusion of the lumen of a bronchus occurred in 26 cases.

It is of interest to note that in no case of bronchiectasis did cerebral abscess occur as a complication. This was first noted by Simpson and confirmed by this work.

#### Cardio-Vascular System.

The pericardium was directly invaded by the growth in 10 cases and the myocardium in 3 cases.

Thrombosis occurred in 1 case, the left innominate and left internal jugular vein being involved.

Direct invasion and obstruction of the superior vena cava by growth occurred in 1 case.

#### Oesophagus.

The oesophagus was invaded in 2 cases and in many other cases the oesophagus was compressed or kinked.

The following Table has been constructed to combine together Group A and Group B and to compare the results with those of other investigators.

TABLE/

TABLE XII.

Complication	Group A. 38 cases	Group A.B. 95 cases	Grove & Kramer 21 cases	Simpson 139 cases	Duguid 175 cases	Wahl 81 cases
Pleura: clear effusion	8	16	3	20		
sanguinous	1	14	3	10		
purulent	13	28	1	9		
malignant	7	23	8	40		26
chronic adhesions	17	34	12			
Broncho-pneumonia	12	25	9			
Bronchiectasis	22	37	3		51**	
Collapse	10	24	7			
Gangrene*	4	8				
Abscess*	2	6	5	16		
Fibrosis	3	7				
Pericardium	10	28	7	62	24	7
Myocardium	3	7	1			
Vessels thrombosis	1	1		24		
Vessels invasion	1	1		16	9	
Oesophagus	2	3		17	10	

\*Most of the abscesses and gangrene cases examined were really of the nature of infective bronchiectatic cavities, resulting from ulceration and obstruction of the bronchi at the site of the primary growth.

\*\*Duguid reported 51 cases with necrotic and suppurating cavities (mainly bronchiectatic in nature) of which 30 cases occurred in the left lung and 21 in the right lung. He accordingly concluded that whereas the right lung is more commonly infiltrated by tumour, the left lung is on the whole more liable to suppuration. This was not confirmed in this series in which both lungs were found equally affected with tumour growth and both sides equally liable to complications.



(5) Histological Features.

## Technique. -

1. Fixation.

To start with the following fixatives were all tried to find which one was the best for my material:

- (1) Helly's modification of Zenker's fluid.
- (2) Corrosive formol.
- (3) 10% formol in normal saline.
- (4) Absolute alcohol.

By doing this, it was found that Helly's modification of Zenker was the best fixative for ordinary routine work and for demonstrating mucicarmine the best was corrosive formol fixation.

The older museum specimens were fixed in Pick's solution and the more recent material in Kaiserling's. Pieces of tissue were taken out of the glycerine preservative, washed for 12 hours in running water and post-fixed in Helly's modification of Zenker.

(2) Embedding and Cutting.

Except for one or two blocks which were cut by the freezing method, the rest were embedded in paraffin and several sections were cut from each block.

(3) Staining.

Haematoxylin and eosin, Weigerts iron haematoxylin/

:toxylin and Van Gieson were used as a routine staining in every case. The following special stains were employed when necessary:

- (a) Mayer's mucicarmine.
- (b) Heidenhain's iron-haematoxylin.
- (c) Heidenhain's azan.
- (d) Verhoff's elastin stain.
- (e) Weigert's elastin stain.
- (f) Foot's stain for reticulum.
- (g) Von Kossa's method for calcium salts.
- (h) Alizarine       "       "       "       "

For the reasons mentioned previously (p.56), classification upon the basis of gross morbid anatomy has been largely abandoned. Classification as to point of origin is unsatisfactory because in the first place few tumours are examined in their early stages, so that the focus of origin is often obscure and secondly there have been no convincing demonstrations of origin from any part of the lung other than the bronchi and bronchioles. However, this point will be discussed under histogenesis (p.110).

Classification upon the basis of the histological character, if histogenic considerations are avoided, is more satisfactory and is the one usually adopted by most authors, since the naked-eye appearances are more/



more or less identical. However, it should be remembered also, that this latter classification is not without its difficulties as the same tumour may present quite different microscopic pictures in different and adjacent areas. Indeed the recognition of this fact was the clue by which Barnard, Duguid and Shennan were able to recognise the carcinomatous nature of what was previously termed "oat-cell sarcoma" of mediastinum. In addition, these authors emphasise and rightly so, the necessity for the employment of large sections, the examination of sections from different parts and the careful search of these sections for parts showing characteristic structure.

A detailed histological description of these tumours is unnecessary in view of the excellent and complete descriptions already published by Barnard, Duguid, Shennan and others. I shall therefore confine myself almost entirely to a consideration of the material which I have studied personally and to the presentation of illustrations made from this material.

Ninety-five cases have been studied in detail histologically by means of sections from different parts and in one case (Case No.21) the growth was early and small so that serial sections of the entire growth were/

were cut, hoping by this means possibly to determine the exact site of origin of the tumour from the bronchial mucosa. However, the tumour was found replacing the entire bronchial mucosa and it was not possible to demonstrate the change over from normal epithelial to malignant cells. In the remaining cases the process had usually advanced as far as to obliterate the early anatomical relationships and accordingly neither whole nor serial sections were employed except in two cases.

Seeing that each author had devised his own classification and adopted his own nomenclature, for example, Shennan has divided his 25 carcinomata into 6 groups based partly on cell type and partly on their origin, I have attempted, for purpose of simplicity to divide the 95 cases into first of all two main groups, namely, differentiated and undifferentiated. The former includes two types: the squamous and the adenocarcinomatous type. The undifferentiated group, in its turn, includes the spheroidal-cell and the tumour which is now commonly described as "oat-cell" carcinoma.

The squamous and adenocarcinomas are readily identified, the former by the arrangement of the cells in columns, the presence of prickly cells and occasionally/



:ally cell-nest formation; the latter by the arrangement of the cells in alveoli with central lumina (see Plate XII and XIII).

PLATE XII Squamous-celled type with cell-nest formation.

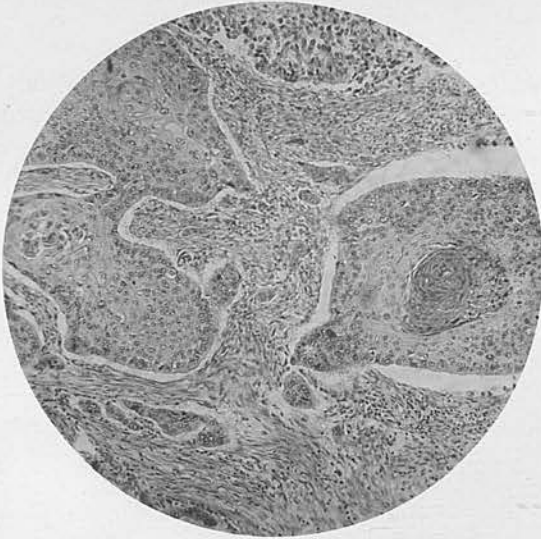
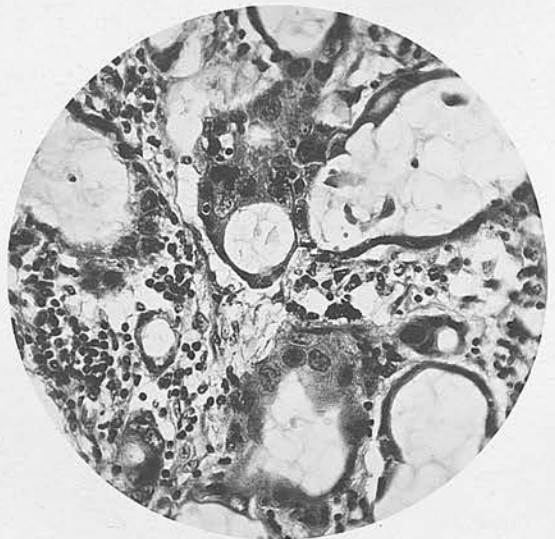


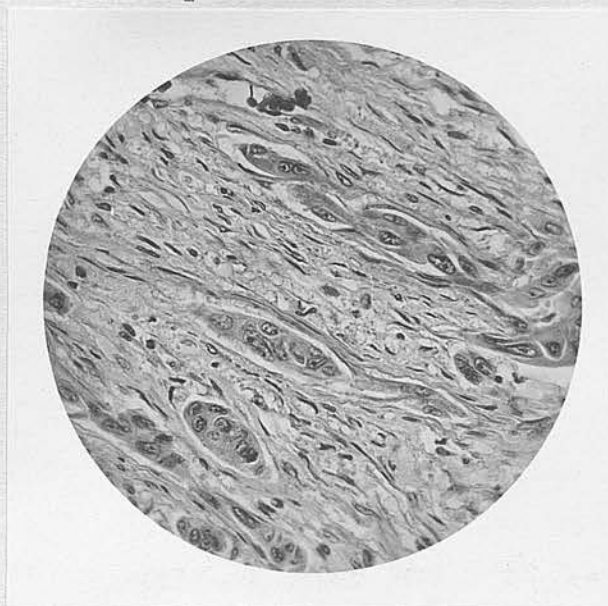
PLATE XIII (x 240) Adenocarcinoma with copious mucus secretion.



Under spheroidal-cell cancers, I have included those cases in which the cells appear in small or large groups supported by a moderate amount of connective tissue. The cell groups do not, as a rule, surround a central lumen, but lie compactly (see Plate XIV).

PLATE/

PLATE XIV (x 240)  
Spheroidal celled.



Under "oat-cell", I have included those cases which are mainly composed of small oval cells, although round and spindle cells are often encountered and occasionally cuboidal and columnar cells. In the literature these tumours have been called transitional cell, oat-cell and small cell carcinomas.

The squamous, adeno-carcinomas and the spheroidal-cell cancers have long been recognised and as mentioned in the section dealing with the gross morbid anatomy have been termed the obvious carcinomata. The cells composing the squamous carcinomata are obvious and have been described above. Those of the differentiated adenocarcinomata/



adenocarcinomata and the undifferentiated spheroidal cell cancers are either large polygonal, cubical or columnar. In addition small oval and spindle cells were found in sections of some of these obvious carcinomata (see Plate XV and XVI), and many showed a curious tendency to the formation of bizarre multi-nucleated giant cells and cells with multiple nuclei arranged around the periphery.

PLATE XV (x 300) Spindle and oval cells in a squamous-celled carcinoma.

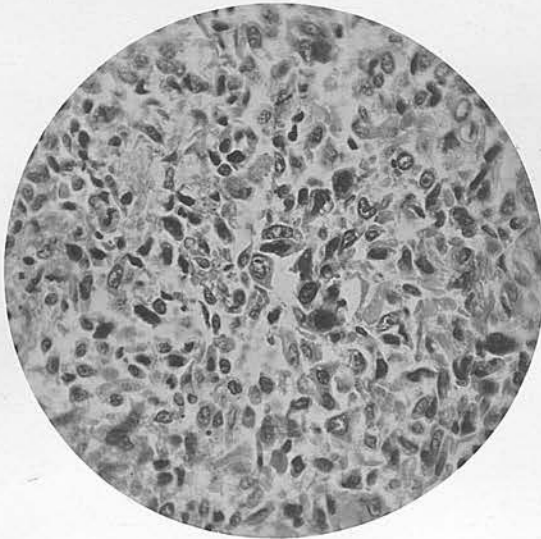
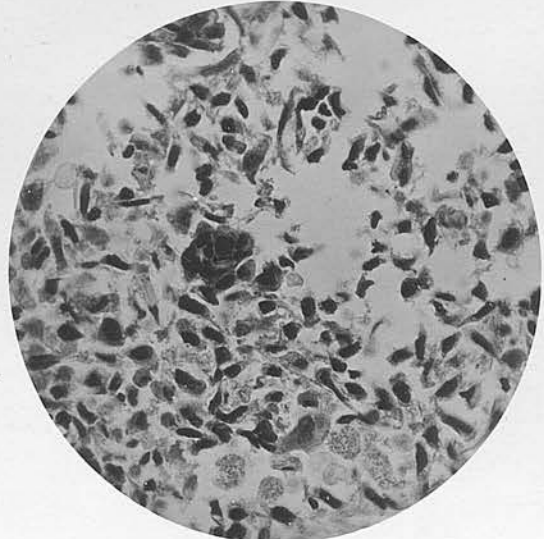


PLATE XVI (x 300) Spindle and oval cells in an adenocarcinoma.



In Case No.26 large malignant cells were seen both in the primary in the lung and in the secondaries in the liver. Many of these cells showed definite evidence of phagocytosis of foreign material such as red/

red corpuscles and leucocytes. In addition there appeared to be what could be termed a digestive vacuole around the ingested material not unlike the digestive vacuole in amoeba. In this connection Willis says "The phagocytic powers of the tumour-cells are debatable. Steinhaus (1891), Stroebe (1892) and others have depicted appearances suggestive of included blood corpuscles or stroma cells within tumour cells; but most workers, including myself have failed to find any unmistakable examples of engulfed host-cells." But the presence of red corpuscles and leucocytes in my case is definite and the question of artefact or inclusion bodies has been definitely excluded and the appearance of the cells is identical with the other tumour cells and does not resemble that of histiocytes (see Plates XVII and XVIII).

PLATE XVII (x 320)



PLATE XVIII (x 320)





Regarding the obvious carcinomata it may be concluded that no hard and fast line can be drawn between the classes especially the adenocarcinomata and the spheroidal-cell cancers. Different parts of the tumour may show different microscopic appearances. In addition Barnard's statement "in obvious carcinomata of the lung "oat-cells" have been found in addition to the more readily recognisable carcinoma cells" has been confirmed.

From the histological point of view the most interesting problem is the nature of the undifferentiated "oat-cell" tumours. These used to be regarded as sarcomas until Barnard in 1926 proved their carcinomatous nature. In view of the fact that they are the most common tumours in my series as well as in those of many other workers, they require a somewhat detailed description.

In this series of 95 cases (Group A.B.) 7 (7.3%) were squamous carcinomata, 14 (14.7%) adenocarcinomata, 8 (8.4%) spheroidal cell carcinomata and 66 (69.4%) were "oat-cell" tumours.

		Cases	%
Differentiated	{ Squamous	7	(7.3)
	{ Adenocarcinomata	14	(14.7)
Undifferentiated	{ Spheroidal-cell	8	(8.4)
	{ "Oat-cell"	66	(69.4)

"Oat/

"Oat-cell" Tumour.Cellular Arrangement.

Practically without exception the undifferentiated "oat-cell" tumours are made up of small oval cells and small round cells, one or the other predominating in different parts of the tumour and its metastases (Plate XIX and XX). The cells are often grouped in small or large islands, bounded by irregular well vascularised septa of connective tissue,

PLATE XIX (x 225) Small oval cells. Note calcification of the blood-vessel.

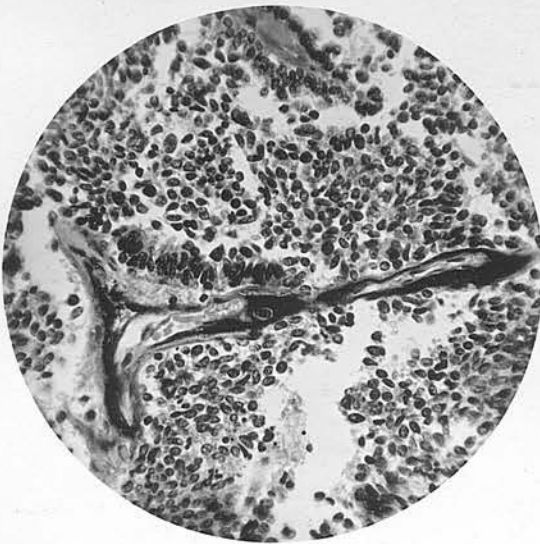
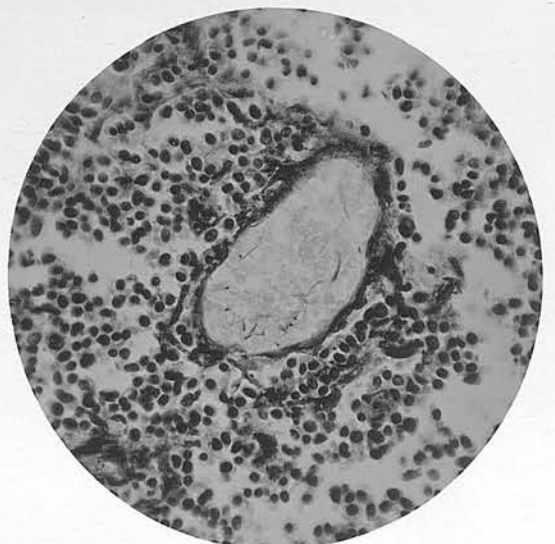


PLATE XX (x 300) Small round cells. Note calcification of the blood-vessel.

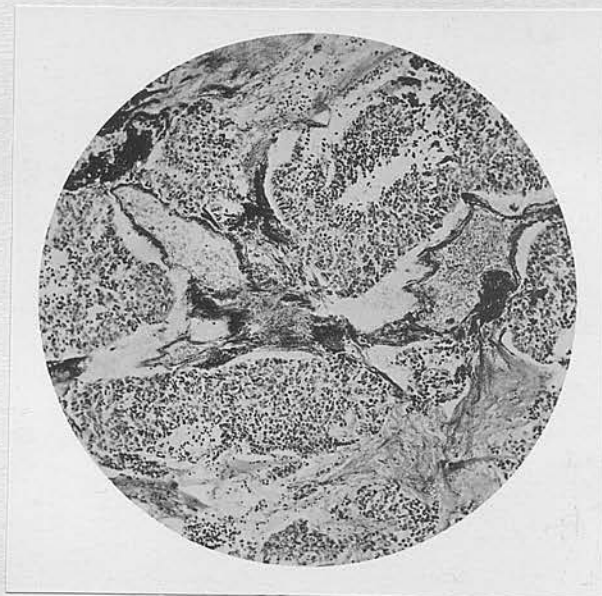


giving the growth an alveolated appearance (Plate XXI). However, the cells may lie loose and separated from each/



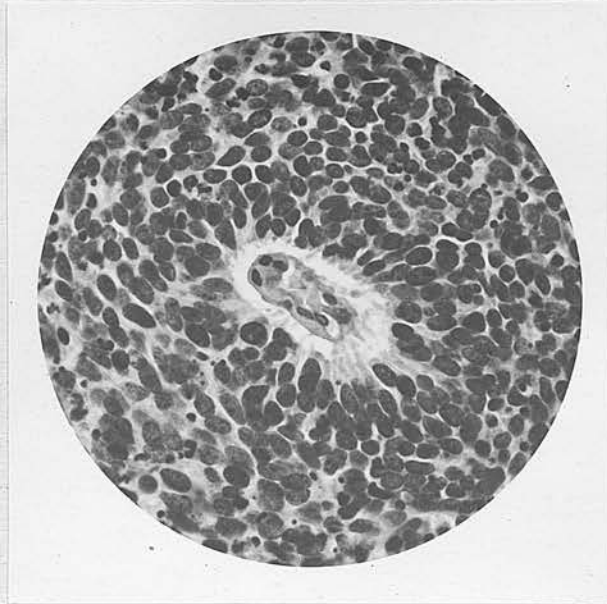
each other (see Plate XIX and XX). In the midst of

PLATE XXI (x 70) Alveolated  
appearance. Note calcification  
of the vessels.

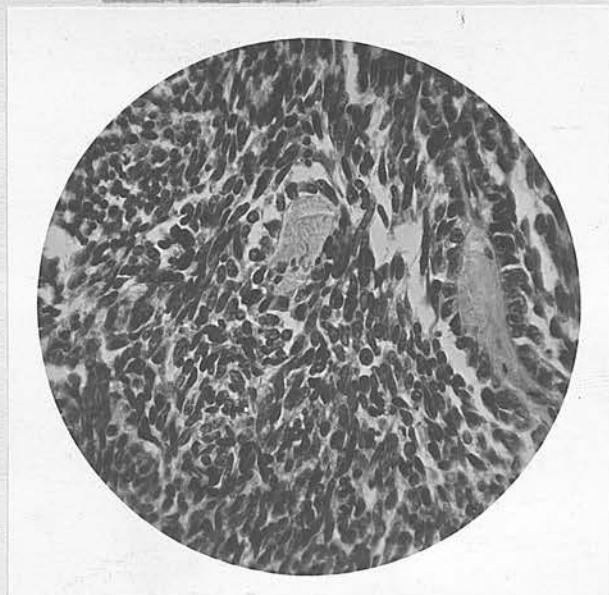


the cell masses there may be a strand of connective tissue with one or more well formed blood vessels and the tumour cells appear to radiate from this fibrous tissue. It is not uncommon to see that the first row of cells are more or less columnar and regular in size (Plate XXII).

PLATE XXII (x 470)/

PLATE XXII (x 470)

Spindle-shaped cells are often seen sometimes in patches and sometimes as isolated cells scattered amongst the oval or round cells (Plate XXIII). Here and there, especially if looked for amongst the

PLATE XXIII (x 275)



"oat-cells" are seen cubical and short columnar cells arranged in rows and attempting to form imperfect alveoli. In other words Barnard's original description of the finding in "oat-cell" tumours of "large polygonal cells indistinguishable from cells of epithelial origin" and of the attempt to form tubules lined by cubical or columnar cells have been seen and amply confirmed, (see Plate XXIV and XXV). It may be added that in the "oat-cell" tumours, in areas a

PLATE XXIV (x 175) Metastatic nodule from an "oat-cell". Note formation of tubules lined by columnar cells.

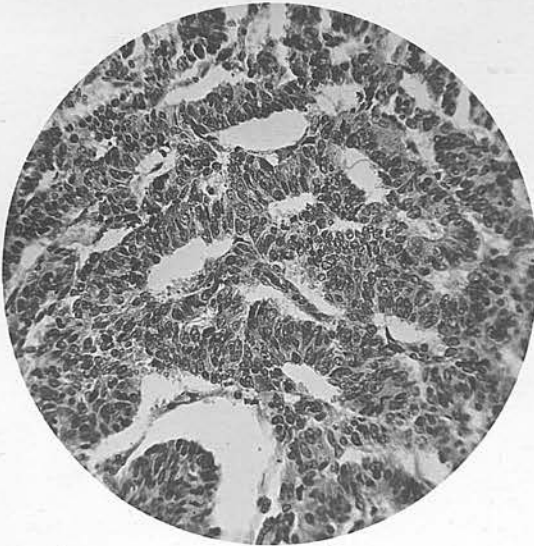


PLATE XXV (x 95) Adenocarcinomatous part in an "oat-cell". Note copious mucus secretion.



certain degree of nuclear palisading is often seen which/

which partly recalls the appearance seen in the Schwannoma. However, it lacks the same regularity of arrangement commonly seen in the latter tumour.

Nuclear character varies greatly. The oval cells usually have vesicular nuclei and the round cells usually densely chromatic nuclei, but the reverse is often seen (Plate XIX, XX and XXII). Mitotic figures are abundant but are often concealed because of the small size of the cell and the richness of the cell in chromatin content. In this connection it may be mentioned that because of the fact that the cells are numerous and rich in chromatin, I was able to foretell the nature of the growth from the mere look of the section when stained with the ordinary haematoxylin and eosin. The sections looked purplish and more deeply stained by the haematoxylin part whereas those of the obvious carcinomata were pinkish and stained more deeply with the eosin.

#### Vascularisation.

The blood vessels are numerous in the primary as well as in the metastatic nodules. They are well formed and appear in delicate or heavy bands of connective tissue throughout the tumour masses.

The/



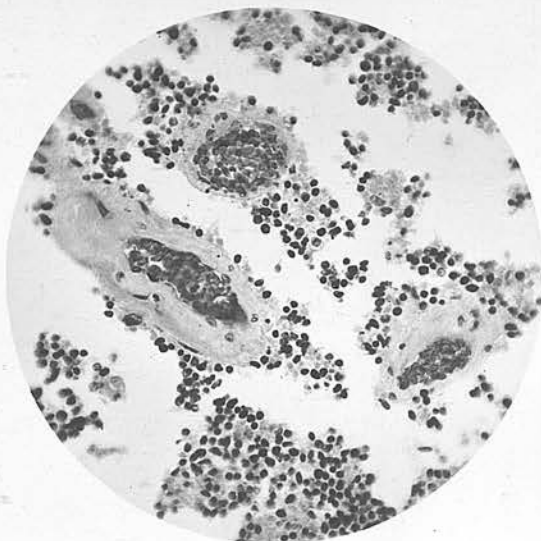
The bare capillaries or vascular slits of sarcomas have not been observed.

Of the 66 "oat-cell" tumours, 32 (48.5%) showed a curious and widespread calcification of the smaller vessels of the tumour, although elsewhere in the lung and in the other organs of the body the vessels did not show such a condition. The presence of calcium was proved by the Alizarine and Von Kossa's method. Besides, these 32 cases which showed definite calcium, many other cases showed a hyaline appearance of the smaller vessels of the growth (see Plate XIX, XX, XXI, XXVI, XXVII, XXIX and XXX). This hyaline appearance

PLATE XXVI (x 125) Note  
calcification of vessels.



PLATE XXVII (x 225) Note  
thickening and hyaline  
appearance of the vessel-walls.



was also observed in the vessels in those cases which showed definite calcification. It is thus, possible that this state of calcification is preceded by hyaline change in the vessel wall. In the early stage, the calcium appears in very fine granules situated in the hyaline looking vessel wall. When well established it forms a dense and compact mass replacing the entire wall. In view of the fact that in many of the early cases only one small block was available for microscopic examination, the above percentage of calcification must be considered as a minimum and accordingly the percentage is probably much higher than 48.5%. This interesting finding which seems not to be mentioned by other workers, curiously enough seems only to be associated with the highly anaplastic oat-cell tumours. Every case belonging to the obvious carcinoma group was thoroughly searched for evidence of calcification in all the available sections and each time I have failed to find either calcification or hyalinisation. In addition, these calcified vessels are often seen in the midst of healthy and well nourished masses of tumour cells and are therefore not necessarily associated.



associated with necrosis and degeneration of the neighbouring tissue. It must occur early, because in case No.41 it occurred in the vessels of the metastasis in the brain and in case No.52 it was seen in the vessels of all the metastases namely kidney, suprarenal, pancreas and lymph-glands.

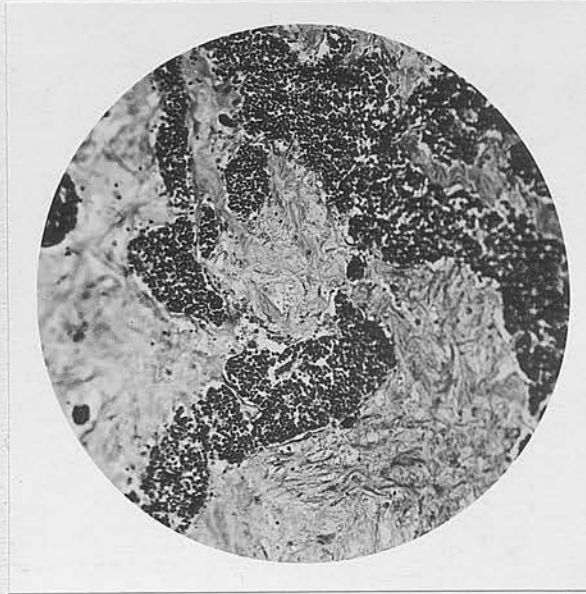
Is this something comparable to the vascular changes met with in the oligodendroglioma? Is it possible to be of use to the radiologist? If so, then it might be helpful in establishing early diagnosis and accordingly early surgical treatment. All of these are questions which I leave in the meantime open for further confirmation by other workers on the subject and till the radiologists get to know of this interesting but rather curious pathological finding in one type of bronchial carcinoma which by far forms the greater percentage of all lung cancers.

#### Desmoplastic Reaction.

The stroma is variable. Usually it is scanty in the oat-cell tumours but sometimes it is abundant. (See Plate XXVIII).

PLATE/

PLATE XXVIII (x 90)  
Excessive desmoplastic  
reaction in "oat-cell".



A good number of the cases have been stained with the Foot's method for reticulum (Plate XXIX and XXX). The cell masses are seen to be devoid of reticulum, whereas if the tumour had been a lymphosarcoma, it would have exhibited an abundant reticulum extending all through the tumour surrounding more or less individual cells.

PLATE/



PLATE XXIX (x 240) Absence of reticulum. Note calcification of the vessels.

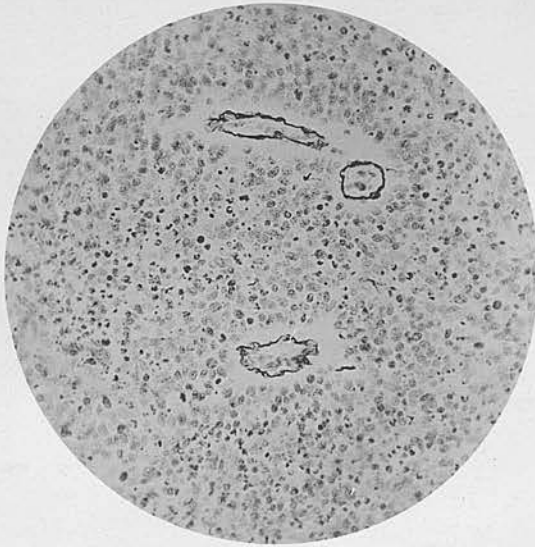
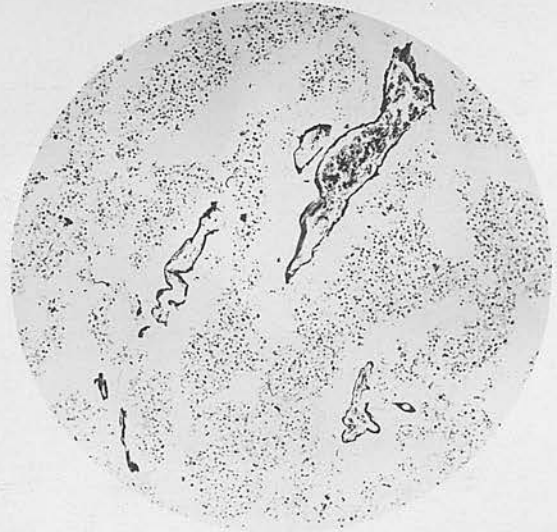


PLATE XXX (x 285) Absence of reticulum. Note calcification of the vessels.



This point (silver impregnation) is stressed by some authors as a necessary means to exclude the tumour from being a sarcoma but it is usually unnecessary to employ silver methods in view of the fact that the true carcinomatous nature of the oat-cell tumour is revealed by other points namely:

- (1) Cellular arrangement.
- (2) Vascularisation.
- (3) Connective tissue relations.
- (4) Gross characters resembling obvious carcinomas.
- (5) Distribution of metastases.

(6) Histogenesis.

The histogenesis of primary cancer of the lung has/

has given rise to much controversy. Indeed this question, alone, would provide material for an extensive general review but will be presented only briefly here, for reasons which are explained later.

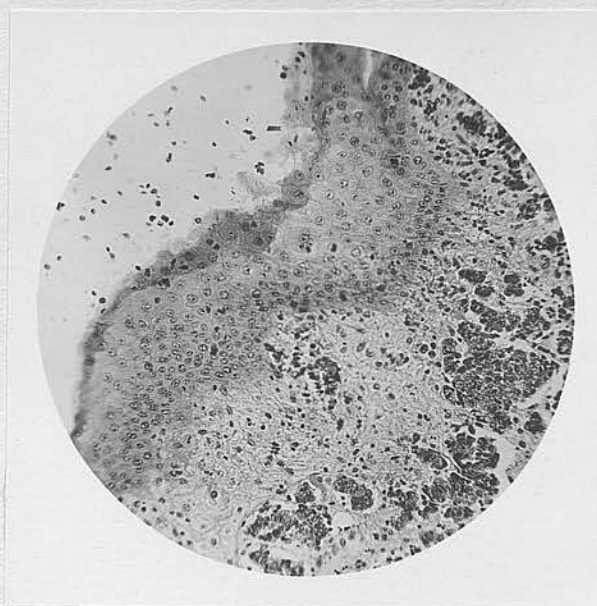
A. Squamous Carcinoma.

The relationship of the squamous carcinoma to metaplasia is well established. It was mentioned under section dealing with "influenza" (p.37) that Askanazy and others have shown that squamous metaplasia in the lower tracheal and bronchial mucosa is of frequent occurrence. In addition, bronchiectatic cavities are especially apt to show it. Thus a carcinoma formed of squamous cells finds a ready explanation. On embryological basis it is to be remembered that the primitive lung bud develops as an outgrowth from a groove in the floor of the primitive pharynx (see Human Embryology and Morphology, by Sir A. Keith, 5th edition, 1933, p.389 under Development of the Pulmonary System) and accordingly the potentiality to revert to a stratified epithelium is always present. But it is not necessary that a carcinoma composed of squamous cells should always follow squamous metaplasia. Plate XXXI shows squamous metaplasia of the bronchial epithelium and yet the growth/



growth is a definite "oat-cell" one.

PLATE XXXI (x 120)  
Squamous metaplasia.



BR. "Oat-cell".

Barnard in 1926 produced considerable evidence to show that the familiar oat-cell tumours of the mediastinum are in reality medullary cancers arising from the bronchi. In 1930, Duguid and Kennedy published two cases stating that mediastinal tumours of other than bronchial origin may show the oat-cell appearance.

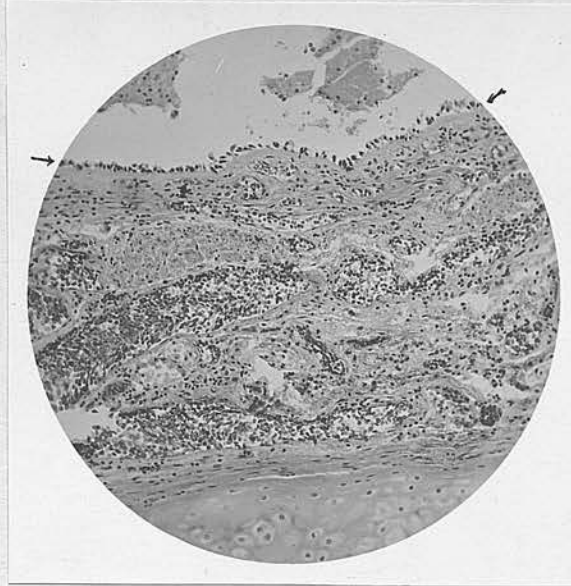
The deductions from my series support Barnard's suggestion and these are the demonstrations naked-eye of the site of origin and the fact that no other tumour/

tumour arising from the mediastinum and containing oat-cells can be found. In addition further evidence of the bronchial origin of the oat-cell tumour, could be gathered from Case No.176. The tumour was circumscribed, about 1" in diameter and arose from the wall of a medium sized bronchus. The rest of the lung tissue was free from tumour and there were no secondary deposits in bronchial or mediastinal glands. Indeed the second of the two cases described by Duguid and Kennedy is in my opinion a primary bronchial carcinoma arising from the middle of the left main bronchus and not arising primarily in the mediastinal lymph glands. The glandular metastases in their case are so enormous as to overshadow the lung tumour.

The bronchial mucous membrane consists of a layer of ciliated columnar cells accompanied by a layer, of small ovoid cells. The latter cells are best seen after the desquamation of the columnar cells in pathological conditions (Plate XXXII). It is believed that these ovoid cells are the mother-cells of the ciliated columnar epithelium. Histologically the oat-cells and the ovoid cells are almost identical and for that reason Maxwell, Ormerod and others have suggested that the "oat-cell" tumours arise from this



PLATE XXXII (x100)  
 Showing desquamation of the  
 ciliated columnar cells and  
 persistence of the small  
 ovoid cells.



layer of small ovoid cells.

C. Adeno-carcinoma and Spheroidal-cell Carcinoma.

Some authors have suggested that the formation of mucin signifies an origin from the bronchial mucous glands and that its absence signifies an origin from the bronchial epithelium. When it is remembered that the lining epithelium of the bronchi is continuous with the epithelium of the mucous glands and that the former contains goblet cells capable of producing mucin, it is impossible to distinguish histologically between tumours that arise from bronchial epithelium and those from the glands and their ducts.

Case/

Case No. 19 (see Plate XXV) was an "oat-cell" tumour, yet it showed a definite adenocarcinomatous area with excessive mucin. In view of the fact that mucin was demonstrated in some of the adenocarcinomas, spheroidal cell cancers and in one oat-cell tumour, it may be concluded that it signifies an origin from the bronchial epithelium or bronchial mucous glands and as stated above it is impossible to distinguish on histological grounds between tumours that arise from the bronchial lining or mucous glands and that the various types encountered are more or less various degrees of anaplasia.

D. Alveolar Carcinoma.

While there is general agreement about the existence of an origin from the bronchial epithelium and bronchial mucous glands, the origin of pulmonary carcinoma from alveolar epithelium has been much debated. This is partly due to the rarity of the condition and partly if not wholly to the unsettled problem of the alveolar lining.

The presence or absence of an epithelium lining the walls of the pulmonary alveoli has been a much discussed subject. Most embryologists, Keith, Frazer and/



and others agree on the method of development of the parenchyma of the lung. According to them the anlage of the lung appears as a spherical vesicle connected with the digestive tract. "The wall of the pocket is lined by a mass of entoderm, which ultimately forms the epithelial lining of the whole respiratory tract, from the ciliated epithelium of the trachea to the pavement epithelium lining the alveoli of the lungs." (Keith, p.390). In addition, most histologists, Cowdry, Schafer and others are agreed that the alveoli are lined by large, flattened cells which form an exceedingly delicate layer, separating the blood capillaries from the air within the alveoli and that amongst the flattened cells are here and there groups of smaller and thicker (cubical) epithelium cells. In favour of an epithelial lining the following is quoted from Cowdry's Special Cytology: "In an atelectatic area of a lung, the alveoli are found to be lined with a continuous cuboidal epithelium and only the absence of smooth muscle prevents their being mistaken, in many instances, for sections of bronchioli. Here, again, the evidence points to a continuous epithelium lining the pulmonary alveoli."

Ogawa in 1920 conducted an extensive study of the comparative histology of the alveolar spaces.

In/

In addition to other material he investigated the lungs of embryo rabbits and concluded "The respiratory epithelium of the rabbit embryo in early stages consists of a single kind of cuboidal cell, and as development proceeds and comes nearer to the final stage, some of them become flatter. In the final stage the respiratory epithelium of all the alveoli consists of a mixture of the two kinds of cells without respiration. The flat cells become flatter at the beginning of respiration. Disappearance of the nuclei of the flat cells takes place in the final embryonic stages and occurs, not suddenly, but gradually by processes of pyknosis, karyorrhexis, etc."

J.S. Young in 1928 produced hyperplasia in the alveolar epithelium of the lung of the rabbit by injecting into the pleural sac a mixture of Sudan III and Sodium Cholate in olive oil.

The authors mentioned above (Keith, Frazer, Cowdry, Schafer and Ogawa) agree that the alveoli are derived from the terminal part of the bronchial tree and that they are lined by epithelial cells. Thus Schafer compares the lung directly to a "compound alveolar gland", in which trachea and bronchial ramifications correspond to duct systems and the air vesicles/



vesicles to glandular alveoli.

Rose in 1928, produced experimental evidence (though incomplete as he mentions himself "the embryonic series is not complete") to show that in the foetuses he studied, a clean-cut distinction between the bronchial tree and the rest of the lung tissue was maintained throughout and that in no stage in the development of the lung could a characteristic glandular arrangement of the alveoli be noticed, an appearance which one would expect if the alveoli were really buds from the terminal part of the bronchial tree. He concluded "Developmentally, the bronchi invade a layer of mesoderm, hence the lung is of dualistic origin. Mesodermal cells form the capillary system, and other mesodermal cells persist as septal cells. The septal cells are probably not epithelial cells, but persistent mesodermal cells spread irregularly among the capillaries. These mesodermal cells should be classed as part of the reticulo-endothelial system. Evidence was not found that the alveoli develop as an outgrowth of the bronchial tree." In other words Rose believes that the alveolus is entirely mesodermic in origin and that it has no epithelial lining.

From the above embryological and histological discussion/

discussion, there are two schools of thought. One school believes in an alveolar lining and the other in its absence. In other words, some believe that the alveolus is lined with an entodermal layer of cells and others believe that the alveolus is entirely mesodermic.

According to the former view, the possibility of a carcinoma arising from such an epithelium is always present. According to the latter, if any tumour arises from such a structure it must be a sarcoma.

Two cases (Nos.37 and 38) in my series are quite different from the others and can fall only under the name of alveolar carcinoma, although the probable origin from a terminal bronchiole cannot be discarded altogether. These two cases present to the naked-eye, the typical appearance of grey-hepatisation of lobar pneumonia. The bronchi are free of any growth (Plate XXXIII and XXXIV). Histologically the tumours are composed mainly of cubical and columnar cells arranged

PLATE/



PLATE XXXIII (Case No.37)



PLATE XXXIV (Case No.38)



in rows and circles around the walls of the alveoli  
and/

and apparently replacing the pavement epithelium.  
Most of these cells show definite cilia (Plate XXXV).

PLATE XXXV (a) (x 350)

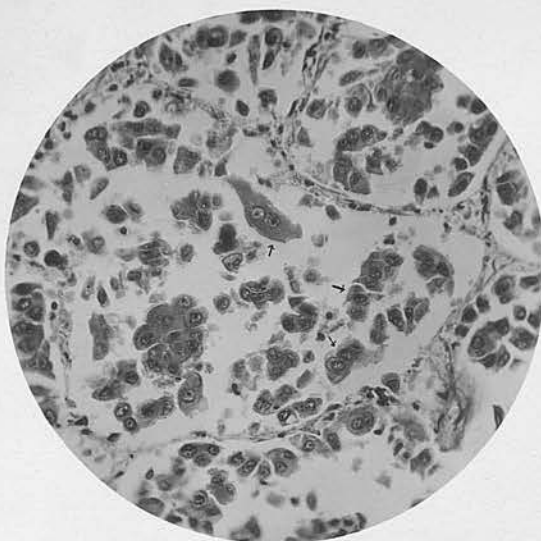


PLATE XXXV (b) (x 1000)



The presence of cilia will certainly weigh more in evidence of them having arisen from a bronchus or bronchiole, although the bronchi in these two cases are free of growth and cilia are not seen in the other 27 obvious carcinomata which occurred in this series of 95 cases. Thus we are left in a rather puzzling situation. Does ciliated epithelium occur in the alveolus? Normally when a section of lung is examined microscopically there appears to be no lining cells/



cells but when stained properly many will agree that there appear flattened cells. Pathologically no one can deny the occurrence of cuboidal and sometimes columnar cells in conditions such as interstitial pneumonia or fibrotic disease of the lung and the glandular structure of the still-born child is familiar to everyone. On examining a section of a lung presenting old bronchiectasis I came across definite cilia in the hyperplastic cells lining the alveoli. The case (No.67) was a bronchial carcinoma squamous in type and confined to the right main bronchus close to its bifurcation. The patient gave a history of long standing bronchiectasis which might have predisposed him to the development of a squamous carcinoma. However, the section was taken from the other lung which was not involved by any tumour growth but was definitely the seat of chronic fibrosis. The epithelium lining most of the alveoli has taken a cuboidal and columnar shape and in many cells definite cilia could be demonstrated by haematoxylin and eosin or better still by Heidenhain's iron-haematoxylin (Plate XXXVI).

PLATE/

PLATE XXXVI (a) (x 80)

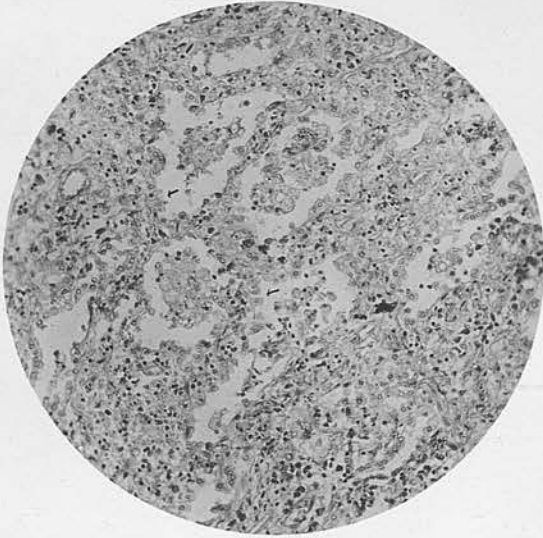


PLATE XXXVI (b) (x 350)

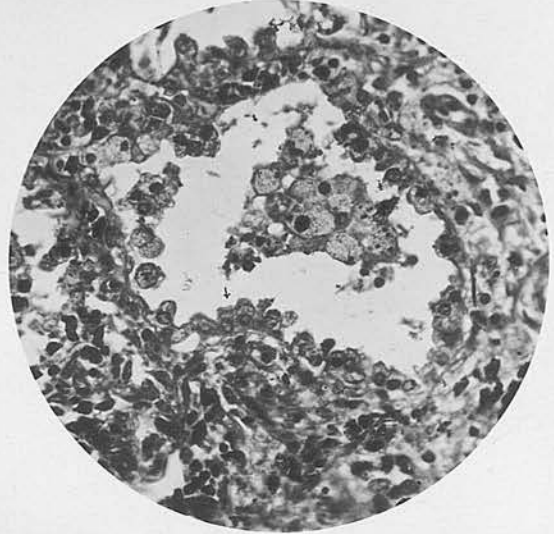
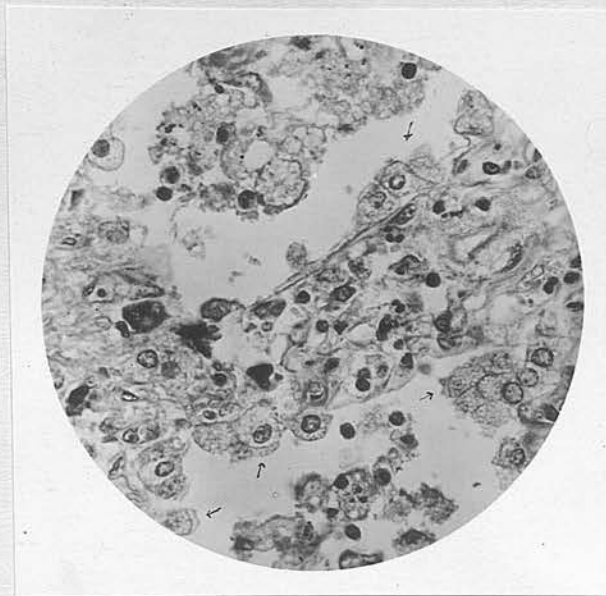


PLATE XXXVI (c) (x 550)



Thus, this accidental finding which was subsequently  
seen/



seen in other cases of fibrotic disease of the lung and in the lung of a still-born child†; threw some light on the disputed question of the alveolar lining. If in conditions when physiological function is no longer needed, the epithelium reverts to its embryological or primitive condition and if it does so by also acquiring cilia, then the probable origin of such cilia is from an entodermal cell. This entodermal cell must come from a pre-existing mother-cell. In the case of the alveolus, this is present in the flattened cell. Accordingly, the flattened cell must be an entodermal cell and only flattened to serve a physiological purpose, namely oxygenation of the blood.

Indeed, if an entodermal lining can be argued for as shown above, then the possibility of an alveolar carcinoma, which is denied by Weller, Schuster and others, exists and my two cases are two examples of it. In other words, two points can be deduced from such an argument, namely:

1. Alveolar carcinoma exists and we have two examples.
2. It is most likely that the alveolus has an entodermal lining.

In/

†I am indebted to Lt.Col. W.F. Harvey of the Royal College of Physicians for lending me this slide.

In addition, if these two cases are agreed upon and accepted as alveolar carcinomata, then the ideal classification of pulmonary carcinoma is one based upon the point of origin - histogenesis - as rising from:

1. Bronchial epithelium.
2. Bronchial mucous glands.
3. Alveolar epithelium.

Lastly as mentioned at the beginning of this histogenic study, the subject is discussed only briefly here as it is intended to go deeply into this question of alveolar carcinoma. The two cases which are available will be examined by cutting whole sections and this new observation on cilia in fibrotic lung disease will be extended and the embryology of the lung alveolus will be investigated more fully as a separate research.



DURATION OF SYMPTOMS AND ERRORS  
OF DIAGNOSIS.

The considerations of symptomatology, diagnosis and treatment are outside of the limits of this study which is intended to deal mainly with the pathological features of primary lung carcinoma and the incidence of this disease in Edinburgh Royal Infirmary. A reference to the duration of symptoms and errors of clinical diagnosis, however, may be made briefly, here.

Duration of Symptoms.

Of the 95 cases (Group A.B.) 5 had no information as to the duration of symptoms. In the remaining 90 cases, the average duration was 7 months, the shortest was one month (5 cases) while the longest was 36 months (one case).

Errors of Diagnosis.

By comparing the ante-mortem diagnosis with post-mortem findings in Group A.B.C., I have ascertained the proportion of cases correctly diagnosed during life in each year of the period 1905-1934 inclusive (Table XIII).

TABLE/

TABLE XIII.

Year.	No. of intra- :thoracic tumours.	Cases correctly diagnosed either as lung cancer or mediastinal tumour.	
		Cases	Percentage
1905	3	0	0
1906	3	2	75
1907	5	1	20
1908	8	2	25
1909	4	1	25
1910	10	2	20
1911	4	0	0
1912	2	0	0
1913	7	3	43
1914	8	4	50
1915	3	0	0
1916	5	1	20
1917	4	2	50
1918	7	3	43
1919	3	2	66
1920	8	3	37
1921	5	3	60
1922	5	2	40
1923	6	4	66
1924	5	4	80
1925	7	4	57
1926	4	1	25
1927	7	3	43
1928	6	4	66
1929	15	9	53
1930	9	5	55
1931	10	8	80
1932	12	5	45
1933	15	8	53
1934	<u>18</u>	<u>14</u>	72
Total	208	Total	102

102 cases were correctly diagnosed out of a total of 208, namely 49 per cent. This figure compares favourably with that of other observers. There does/



does not appear to be any marked improvement in the clinical diagnosis and in view of the fact that in Edinburgh the statistical studies do not show an increased incidence of primary lung carcinoma, it may be concluded that there occurred only a shift in the diagnosis, namely from mediastinal sarcoma to bronchial carcinoma.

The following Table XIV (in order of frequency) is an analysis of those cases incorrectly diagnosed in life and discovered to be carcinoma of the lung only at autopsy (106 cases).

TABLE XIV.

	Cases.
?	25
Phthisis	16
Bronchitis, Bronchial Asthma and Heart-failure	11
Broncho-pneumonia, Lobar Pneumonia and Empyema	8
Gastric Carcinoma	6
Aneurysm of Aorta.	5
Gumma of Cord, Transverse Myelitis and Tabes Dorsalis	5
Carcinoma of large intestine	4
Encephalitis lethargica	4
Tumour of spine	3
Bronchiectasis	2
Carcinoma of liver	2
Cerebral Thrombosis	2
Intrathoracic Goitre	2
Lung Abscess	2
Tuberculoma	1
Atrophic Cirrhosis of liver	1
Acute haemorrhagic pancreatitis	1
Gall-stones	1
Splenic anaemia	1
Septicaemia	1
Pathological fracture of femur	1
Sciatica	1
Nervous dyspepsia	1
Total	106

From the above table it is seen that in the majority of cases the diagnosis was that of a complication, the primary carcinoma being undetected.



"SARCOMA."

It has already been shown that many of the tumours previously designated "oat-cell sarcomata" of the lung or of the mediastinum have had their origin from bronchial epithelium. In recent years, there is an inclination to push the sarcomas into the background and even to exclude them altogether from among pulmonary growths.

In this extensive study two cases were identified microscopically as spindle-cell-sarcomas. In one case (No.2 Miscellaneous Group) which occurred in 1927 the post-mortem notes were incomplete but blocks were available and microscopically the structure was that of a spindle-cell-sarcoma. In the second case (No.1 Miscellaneous Group) which occurred in 1933 the lung was thoroughly examined and no obvious origin in the bronchial tree could be seen. (See Plate XXXVII).

PLATE XXXVII:

Primary Lung Sarcoma (spindle-cell).





In view of the fact that only 2 cases of sarcoma occurred over a long period, it may be concluded that primary sarcoma of the lung does exist, though its occurrence is rare.



CONCLUSIONS.

1. In Edinburgh Royal Infirmary, intrathoracic neoplasm (for meaning of term see page 6) forms about 1.3 per cent of all cases at autopsy and 8.3 per cent of all malignant diseases discovered at post-mortem.
2. An analysis of post-mortem records at Edinburgh Royal Infirmary has shown that there has been no increase during 31 years in the incidence of intrathoracic neoplasm compared with total post-mortems, total tumours in all sites, total admissions or total deaths and that the rise noted in the last year or two is unlikely to be of any significance unless it continued and was sustained for several more years.
3. Primary lung carcinoma occurs more frequently in Edinburgh in men than in women in the proportion of 5:1.
4. There appears to be no relation between occupation and the disease in Edinburgh; and no relation between occupation and lung carcinoma is known except in so far as the Schneeberg and Joachimstal mines are concerned.
5. Macroscopically the various types of primary bronchial carcinoma are very much alike and there is no relation between the type of growth and the amount of mediastinal infiltration.
- 6./

6. The formation of mucin does not necessarily prove that the carcinoma takes origin from the bronchial mucus glands.
7. The pathology of the "oat-cell" bronchial carcinoma is more or less fully described and a curious calcification of the smaller vessels in these tumours has been noted.
8. Arguments advanced in favour of the existence of alveolar carcinoma (2 cases described).
9. Sarcoma of the lung may occur (2 cases described).

ACKNOWLEDGEMENTS. I desire to record my grateful thanks to Professor A.M. Drennan at whose suggestion this work was undertaken and for his constant help and criticism. I also wish to thank Lt.Col. A.G. McKendrick for the trouble he has taken to revise the statistical part. I am indebted to Mr. T.C. Dodds for the photographs.



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